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IN THE

Supreme Court of the United States

OCTOBER TERM, 1991

GENETICS INSTITUTE, INC.,
AND CHUGAI PHARMACEUTICAL CO., INC.,
Petitioners,

v.

AMGEN, INC.,
Respondent.

PETITION FOR WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR WRIT OF CERTIORARI

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July 1, 1991

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QUESTIONS PRESENTED

1. May a federal court exempt the inventors of genetically engineered life forms (in this case, hamster cells fused with human genetic material) from the full disclosure requirements of 35 U.S.C. §§ 112 and 114 which assure, pursuant to Article I's Patent Clause, that those who seek the benefits of patent monopoly give up the benefits of trade secrecy?

2. Independently, may a federal appeals court shift to the holder of a challenged patent the burden of proof imposed on the challenger by 35 U.S.C. § 282, and then substitute its own factual findings for those of the trial court, contrary to Fed.R.Civ.P. 52(a) and the decisions of this Court?

PARTIES TO THE PROCEEDING

The names of all parties appear in the caption. Neither Genetics Institute nor Chugai Pharmaceutical has a parent company or any non-wholly-owned subsidiaries.

TABLE OF CONTENTS

QUESTIONS PRESENTED i

PARTIES TO THE PROCEEDING iii

TABLE OF AUTHORITIES vii

OPINIONS BELOW 1

JURISDICTION 1

CONSTITUTIONAL AND STATUTORY PROVISIONS AND RULE INVOLVED 1

STATEMENT OF THE CASE 1

A. Recombinant DNA Technology 4

B. Respondent Amgen's Genetic Engineering Patent 5

C. Petitioner GI's Purified Hormone Patent . . 7

D. Proceedings Below 8

REASONS FOR GRANTING THE WRIT 12

I. The Federal Circuit's Distinction Between Genetically Engineered Life Forms And All Other Inventions Contravenes The Patent Laws Enacted By Congress, Exceeds The Institutional Limits On The Judiciary Affirmed In *Diamond* v. *Chakrabarty*, And Undermines The Constitutional Policy Of Promoting The "Progress Of Science And The Useful Arts" . 12

A. 35 U.S.C. § 112 Requires All Patentees To Give Up Trade Secret Protection On The Best Mode Of Their Inventions 13

B. Congress' Best Mode Requirement Makes No Distinction Between Natural And Genetically Engineered Life Forms And The Federal Circuit Has No Authority To Enact Such A Distinction 14

TABLE OF CONTENTS (cont.)

C. The Decision Below Effectively Exempted Genetically Engineered Life Forms From The Best Mode Requirement By Upholding Respondent's Refusal To Deposit Its Cell Line . . . 16

1. The Rationale for the Federal Circuit's Judge-Made "No Deposit" Rule for Artificial Life Forms Is Deeply Flawed 18

2. The Federal Circuit Confused the Best Mode and Enablement Requirements of the Statute 22

D. The Federal Circuit Diluted Congressional Condemnation Of An Inventor's Concealment Of His Best Mode 23

E. The Federal Circuit's Rejection Of The Usual Remedy Of Patent Invalidation In This Setting Will Prove To Be Particularly Pernicious In The Field Of Genetic Engineering 25

II. The Federal Circuit's Shifting Of The Burden Of Proof To The Patent-Holder, And Its Substitution Of Its Own Factual Findings On GI's Patent For Those Of The District Court, Violate 35 U.S.C. § 282 And Conflict With *Anderson* v. *City of Bessemer* And Fed.R.Civ.P. 52(a) 27

CONCLUSION 29

TABLE OF AUTHORITIES

Cases:

Amgen Inc. v. *U.S. Int'l Trade Comm'n*, 902 F.2d 1532 (Fed.Cir. 1990) 15

Anderson v. *City of Bessemer*, 470 U.S. 564 (1985) 29

Application of Argoudelis, 434 F.2d 1390 (C.C.P.A. 1970) 15,17, 19,21

Application of Nelson, 280 F.2d 172 (C.C.P.A. 1960) 18

Bonito Boats, Inc. v. *Thunder Craft Boats, Inc.*, 109 S.Ct. 971 (1989) 13

Chas. Pfizer & Co., Inc. v. *FTC*, 401 F.2d 574 (6th Cir. 1968), *cert. denied*, 394 U.S. 920 (1969) . . . 24

Chemcast Corp. v. *Arco Industries Corp.*, 913 F.2d 923 (Fed.Cir. 1990) 25

Consolidated Aluminum Corp. v. *Foseco Int'l Ltd.*, 910 F.2d 804 (Fed.Cir. 1990) 24

Dale Electronics, Inc. v. *R.C.L. Electronics, Inc.*, 488 F.2d 382 (1st Cir. 1973) 24

Dana Corp. v. *IPC Ltd. Partnership*, 860 F.2d 415 (Fed.Cir. 1988), *cert. denied*, 490 U.S. 1067 (1989) 13,22,25

Diamond v. *Chakrabarty*, 447 U.S. 303 (1980) . . 2,4, 15,16

Edwards v. *California*, 314 U.S. 160 (1941) . . . 26

Ex parte Forman, 230 USPQ 546 (PTO Bd. of App. and Interferences 1986) 20

Ex parte Jackson, 217 USPQ 804 (PTO Bd. of App. 1982) 21

Ex parte Kropp, 143 USPQ 148 (Pat.Off.Bd. of App. 1959) 20,21

TABLE OF AUTHORITIES (cont.)

Feldman v. *Aunstrup*, 517 F.2d 1351 (C.C.P.A. 1975), *cert. denied*, 424 U.S. 912 (1976) 19,20,21

In re Gay, 309 F.2d 769 (C.C.P.A. 1962) 17,22

In re Lundak, 773 F.2d 1216 (Fed.Cir. 1985) . . . 16,19,21

Kewanee Oil Co. v. *Bicron Corp.*, 416 U.S. 470 (1974) 13,14

Kingsland v. *Dorsey*, 338 U.S. 318 (1949) 23

Northern Telecom, Inc. v. *Datapoint Corp.*, 908 F.2d 931 (Fed.Cir.), *cert. denied*, 111 S.Ct. 296 (1990) 25

Panduit Corp. v. *Dennison Mfg. Co.*, 810 F.2d 1561 (Fed.Cir.), *cert. denied*, 481 U.S. 1052 (1987) . 29

Ralston Purina Co. v. *Far-Mar-Co., Inc.*, 772 F.2d 1570 (Fed. Cir. 1985) 27

Spectra-Physics, Inc. v. *Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir.), *cert. denied*, 484 U.S. 954 (1987) . 22,25

SRI Int'l v. *Matsushita Elec. Corp. of America*, 775 F.2d 1107 (Fed.Cir. 1985) 26

Union Carbide Corp. v. *Borg-Warner Corp.*, 550 F.2d 355 (6th Cir. 1977) 16,23

***Constitutional Provisions, Statutes, and Rules*:**

The Patent Clause, Art.I, § 8, cl.8 . . . . . 2,13, 14,30

35 U.S.C. § 101 15,16

§ 112 . . . . . *passim*

§ 114 2,5,19

§ 162 15

§ 282 27

TABLE OF AUTHORITIES (cont.)

Patent Act of April 10, 1790, ch. 7, § 6, 1 Stat. 109 14

Patent Act of Feb. 21, 1793, ch. 11, §§ 3 & 6, 1 Stat. 318 14

Patent Act of July 8, 1870, ch. 230, § 26, 16 Stat. 198 14

Patent Act of July 19, 1952, ch. 950, § 1, 66 Stat. 798 14

Federal Rule of Civil Procedure 52(a) 27,29

***Miscellaneous*:**

I. Cooper, *Biotechnology and the Law* (1991) . . . 21

52 Fed.Reg. 34080 (Sept. 8, 1987) 10

Halluin & Wegner, *Biotechnology Practice After Amgen and Scripps*, American Intellectual Property Law Ass'n Biotechnology Litigation Report (March 1991) 12

Manual of Patent Examining Procedure 6

Brief Amicus Curiae of the American Society for Microbiology in *Diamond* v. *Chakrabarty*, No. 79-136 13

Virology, July 1991 22

OPINIONS BELOW

The opinion of the United States Court of Appeals for the Federal Circuit is reported at 927 F.2d 1200 and is reprinted as Appendix A. The memorandum and order of the United States District Court for the District of Massachusetts (Saris, U.S.M.), are reported at 13 USPQ2d 1737 and reprinted as Appendix B. The earlier decision of the District Court is reported at 706 F.Supp. 94 and reprinted as Appendix C. The final judgment of the District Court on all issues is reprinted as Appendix D.

JURISDICTION

The decision of the Court of Appeals was entered on March 5, 1991. A timely petition for rehearing was denied on April 2, 1991. *See* Appendix E. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

CONSTITUTIONAL AND STATUTORY PROVISIONS AND RULE INVOLVED

The Patent Clause, Art. I, § 8, cl. 8, the relevant portions of 35 U.S.C. §§ 112, 114, 282, and Fed.R.Civ.P. 52(a) are set forth in Appendix G.

STATEMENT OF THE CASE

This case raises a question likely to be of enduring significance as science and technology transform the social, medical, and economic landscape: how far may federal courts go in responding to new technologies by revising the balance Congress struck long ago among competing values and interests?

That question arises here in a context that is itself of singular social significance, for this case involves a patent monopoly

governing the production, by means of genetic engineering, of erythropoietin (EPO), the hormone that enables the human body to make red blood cells. Administration of EPO provides life-saving or life-enhancing treatment for those suffering from anemia, kidney failure, and other disorders. At stake is whether an inventor may retain a 17-year patent monopoly on this means of producing life-sustaining EPO while refusing to place in a public depository — and therefore in the public's hands — a sample of the laboratory-created cell line that constitutes the best mode for practicing this genetic engineering invention.

American patent law, reflecting the progress-promoting focus of the Patent Clause, Art. I, § 8, cl. 8, is distinctive in putting each inventor to a choice between receiving a patent monopoly and preserving as a trade secret the "best mode contemplated by the inventor of carrying out his invention." 35 U.S.C. § 112. The act of Congress embodying this social contract makes an explicit exemption for asexually produced plants but does not otherwise distinguish among types or categories of inventions. Indeed, in *Diamond* v. *Chakrabarty*, 447 U.S. 303 (1980), this Court expressly held that the task of crafting such distinctions belongs to Congress, not the judiciary.

Where the invention at issue comprises useful biological material, both the Patent Office — to which Congress has delegated the authority to decide when samples of proposed inventions must be placed on deposit, *see* 35 U.S.C. § 114 — and the appellate courts have consistently interpreted § 112 to require that a sample of this cellular material be made accessible to the public by placement in a recognized depository, such as the American Type Culture Collection (ATCC). The rationale for deposits has been that it may be impossible to describe the qualities of the biological material with mere words and to assure public access to the material with only a written account of the procedures used to obtain or create it. Such deposits fulfill both ends of § 112's best mode requirement: (1) during the 17-year patent monopoly, other scientists

wishing to experiment with, refine or improve upon the invention will be able to start from (rather than have to rediscover) the inventor's best mode; and (2) when the patent expires, the full fruit of the invention at the time the patent application was filed will be placed in the public's hands for all to begin using without further delay.

Despite this well-established body of statutory and administrative law, the Court of Appeals for the Federal Circuit held in this case that everything turns on the *technology* through which one obtains novel biological material. It stated that this case "presents . . . a question of first impression concerning the best mode requirement for patents involving novel genetically engineered biological subject matter." (A19).[1] It observed that past cases insisting on deposit of novel biological material happen to have involved "natural" materials extracted from nature: for example, where an inventor isolates unusual microbes from soil samples and applies screening procedures to obtain cells that secrete useful antibiotics, the inventor must deposit samples of his special drug-producing cells rather than merely explain where he found the soil and what lab procedures he used.

Despite the far more complex, challenging and elaborate procedures involved in genetic engineering, the Federal Circuit held that there is no requirement that *any* biological material be deposited when "artificial" materials are created in the laboratory. The court of appeals appeared to act on the curious assumption that creating a new life form by means of recombinant DNA technology (here, fusing the genetic material of human beings and hamsters to create cells capable of mass-producing a life-saving human hormone) is a simple matter of following a set of written instructions. No deposits of such revolutionary life forms need be made, we are told, because other scientists supposedly can just grow something like them

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[1] Citations to the appendix to this petition will be styled "A___." Citations to the appendix filed with the Federal Circuit will be styled "Fed.Cir.App. ____."

in their own labs. Thus the court below held that a genetic engineer, unlike all other inventors, may keep his best mode cell line as a proprietary trade secret. No policy-making body — not Congress, not the Patent Office, not the Food and Drug Administration — has proceeded on any such perverse hypothesis; it is the brainchild of the Federal Circuit alone.

A. Recombinant DNA Technology

In *Chakrabarty*, this Court upheld the patentability of a living microorganism (an *E. coli* bacterium) altered through genetic engineering. That ruling breathed life into the biotechnology industry and led to the creation of dozens of firms and the investment of billions of dollars. The overwhelming commercial focus of this industry to date has been on creating microorganisms that function as miniature "cell factories" to manufacture mass quantities of valuable human proteins for medical applications. This case involves erythropoietin (EPO), a hormone secreted primarily by the kidneys that triggers the production of red bloods cells. (A49). Treatment with EPO raises red blood cell levels, thereby eliminating the need for costly and risky blood transfusions for those suffering from anemia — particularly those with kidney disease who do not produce enough of their own EPO, but also those undergoing chemotherapy, AIDS victims, and others. EPO is therefore the key both to saving the lives of and dramatically improving the quality of life for many people.

Human proteins such as EPO are chains of amino acids constructed in the body by specialized cells that function as factories, joining one amino acid to another until a chain is complete, then moving on to assemble another chain. The operation of each specialized assembly line is controlled by a particular gene (a segment of the genetic material DNA), contained in the nucleus of the cell. This gene specifies the order of amino acids for each type of protein and causes the cell to produce that protein. (A51-A52).

A primary aim of genetic engineering is to create *surrogate cell factories*: special "host cells" that have been artificially programmed by the insertion of a human gene and thereby induced to manufacture the desired protein in mass quantities. Although the technology is sophisticated and difficult to develop, the basic idea is easily understood. First, the particular genetic sequence that controls cellular production of EPO is identified. Second, that EPO gene is isolated from the hundreds of thousands of other genes contained in human DNA and stabilized by being joined to a "plasmid" or "vector." Finally, this vector is inserted into a suitable "host cell," thereby instructing that cell how to make EPO; a host cell modified in this way is said to be "transfected". (A56). Commercial use of this technology involves transfecting millions of host cells with the EPO gene and then selecting a "cell line" that, all relevant factors considered, is the "best mode" of producing EPO. Many copies of these individual cells are then created, and these copies are in turn used to produce EPO in mass quantities. (A56-A59).

B. Respondent Amgen's Genetic Engineering Patent

The patent at issue in the first question presented is U.S. Patent 4,703,008, entitled "DNA Sequences Encoding Erythropoietin" (the genetic engineering patent), issued on October 27, 1987, to Dr. Fu Kuen Lin, an employee of respondent Amgen Inc. (Amgen). The claims of this patent cover the following tools for producing EPO for therapeutic use in human beings: (1) the isolated DNA sequence for EPO; (2) vectors for transporting this EPO gene into host cells; and, most importantly, (3) host cells transfected with this EPO gene. (A217). These host cells constitute the ultimate invention of Amgen's genetic engineering patent: the cell factories that actually produce EPO for use in treating blood disorders.

Section 114 of Title 35 empowers the Patent Office, "[w]hen the invention relates to a composition of matter, . . . [to]

require the applicant to furnish specimens or ingredients for the purpose of inspection or experiment." Accordingly, as the district court explained:

> The *Manual of Patent Examining Procedure*, § 608. 01(p)(C) (the Manual), provides that patent applicants whose inventions depend on the use of microorganisms or other biological material "must take additional steps to comply with the requirements of 35 U.S.C. § 112" when the microorganisms or other biological material are not known and readily available to the public. These additional steps include the making of a deposit of the microorganism or other biological material in a depository that is readily accessible to the public . . . .

(A122).

The only cell deposits made in the ATCC by or on behalf of Dr. Lin by the time the patent application was filed on November 30, 1984, were deposits of conventional *E. coli* and yeast cell strains that had not even been transfected with the EPO gene. (A128, A130). Lin deposited neither the vectors used to carry the EPO gene into a host cell nor any transfected host cells (the microorganisms that actually produce the EPO). Lin's patent claims were rejected by the Patent Examiner on July 3, 1986 for failure to make a satisfactory deposit:

> The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure. The invention depends on certain specific plasmids/microorganisms. As such, a deposit is required under 35 U.S.C. § 112.

U.S. Patent Application Serial No. 675,298, Prosecution History at 179 (First Rejection, July 3, 1986) (Fed.Cir.App. 26,009) (*quoted in* A131).

Although Amgen objected to the Examiner's conclusion that "the 'invention depends on certain specific plasmids/microorganisms,'" it assured the Patent Examiner that the ATCC would receive appropriate cell deposits and on that basis urged that "all requirements of the first paragraph of § 112 are met, [and] that the objection to the specification should be withdrawn." Prosecution History at 208 (Oct. 2, 1986) (Fed.Cir. App. 26,038).

One week before Amgen's genetic engineering patent issued, Dr. Lin deposited with the ATCC a bacterial virus containing the human EPO gene, and an *E. coli* bacterial host cell transfected with a monkey EPO gene. (A128-A129). Neither deposit provided any working human EPO host cell, since EPO obtained from bacteria is not bioactive in the human body and is therefore of no therapeutic value to human beings. (A130). Only mammalian host cells can produce EPO for use in human beings.

Meanwhile, petitioner Genetics Institute (GI) had also been working to isolate the human EPO gene and to create host cells to produce EPO.[2] Thus this case, as the district court noted, "is about the highly competitive race between two leading biotechnology companies, among others, to clone the gene for the human hormone EPO." (A39). The salient difference between the participants in this race is that, while Amgen refused to deposit samples of the mammalian cell line that constituted its "best mode" for producing EPO, it is undisputed that petitioner GI deposited samples of *both* of the transfected host cell lines it had developed. Trial Transcript Vol. 26, pp. 109-116.

C. Petitioner GI's Purified Hormone Patent

While Amgen won the race to isolate the EPO gene, GI was the first to invent homogeneous EPO — that is, to identify

[2] Respondent Amgen filed its genetic engineering patent application on November 30, 1984; GI filed its competing genetic engineering patent application, No. 693,258, a few weeks later, on January 3, 1985.

the characteristics of a purified EPO composition suitable for treatment of human patients. On June 30, 1987, Dr. Rodney Hewick of GI was granted U.S. Patent 4,677,195, entitled "Homogeneous Erythropoietin" (the purified hormone patent), a patent that is exclusively licensed to petitioner Chugai Pharmaceutical Co., Ltd. (Chugai) of Japan. Thus, while Amgen held a patent on the intermediate tools for production of EPO by recombinant DNA technology, GI held an earlier patent on homogeneous EPO such as that produced and ultimately purified by Amgen for pharmaceutical use.

D. Proceedings Below

On the same day that its genetic engineering patent was issued, Amgen filed suit against petitioners GI and Chugai claiming that they infringed that patent by using transfected mammalian host cells containing vectors with DNA coding for the production of human EPO, and further claiming that GI's purified hormone patent was invalid. (A6). Among other defenses, petitioners argued that Amgen's genetic engineering patent was invalid for failure to comply with the best mode requirement of 35 U.S.C. § 112 because Dr. Lin failed to "set forth" the "best mode" host cells known to him as of November 30, 1984, the date he filed the patent application. (A16-A17).

The district court deemed it an "extremely close" question "whether the best mode was adequately disclosed in the patent specification." (A127). The court found that, by the date he filed his patent application, Dr. Lin knew "that the best way to express EPO was from mammalian cells, not yeast cells or *E. coli* cells," and that a transfected host cell line derived from a certain Chinese hamster ovary (CHO) cell strain (CHO B11 3, .1) was the best mode of the invention and was, in fact, slated to be used for Amgen's master working cell bank in the commercial production of EPO. (A128). "Despite this knowledge," the district court stressed, "*Dr. Lin never deposited any mammalian host cell strain, including any CHO cell, with*

the ATCC." (A128-A129) (emphasis in original). This refusal to deposit mammalian host cells occurred "despite the Patent Examiner's specific request that a deposit be made." (A131):

> [Amgen] has never adequately explained why *E. coli* and yeast cells, which are available to the scientific community, were deposited, but not the best mode mammalian cells. The failure to deposit a CHO cell despite the [Patent Office] Manual provision and the Patent Examiner's directive, particularly in light of Amgen's willingness to deposit other kinds of host cells, constitutes evidence of concealment of the best mode.

(A131). The significance of this refusal to deposit was underscored by the district court's finding that, without a deposit, "no scientist could ever duplicate exactly the best mode used by Amgen." (A132).

The district court nevertheless held that Amgen had fulfilled the best mode requirement because the patent *described how to hunt for something like* the best mode cells: the genetic engineering techniques of gene amplification and limited dilution cloning described in Example 10 of the patent (*see* Appendix F), when considered along with the patent's disclosure of the EPO production rates of CHO cells amplified at an MTX concentration of 100 nanomolar, were sufficient to enable "those of ordinary skill in the art [to] produce mammalian host cell strains or lines with similar levels of production." (A132).

As to GI's purified hormone patent, the district court held in its first opinion (Appendix C) that Amgen's EPO produced by recombinant DNA technology, when purified to homogeneity for treating human patients, infringed this GI patent. (A212). The district court later held that "Amgen had failed to establish by clear and convincing evidence that [GI's patent] specification fails to enable one skilled in the art to obtain a pure EPO composition . . . meeting the [patent's] 160,000

IU/AU specific activity test for 'homogeneous' EPO." (A185).[3] All of Amgen's examples of instances in which scientists had failed to obtain EPO of the required purity were rejected as meaningless because Amgen failed to establish that those scientists had in fact followed the process disclosed in GI's purified hormone patent. (A185-A186).

The Court of Appeals for the Federal Circuit affirmed the district court's holding that Amgen had met the best mode requirement with respect to its genetic engineering patent despite the lack of a deposit, describing the issue as one of first impression. (A19). The court noted that deposits of *naturally occurring* microorganisms have been required for many years by both the Patent Office and the courts "when a written description alone would not place the invention in the hands of the public and physical possession of a unique biological material is required." (A19). The court also noted that Patent Office guidelines provide that "[i]f a deposit is the only way to comply with the best mode requirement then the deposit must be made." (A22) (quoting 52 Fed.Reg. 34080, 34086) (Sept. 8, 1987).

But Chinese hamster ovary cells containing the human EPO gene do not occur in nature: they are a life form created for the first time by artificial means in the laboratory. And the court decided that the settled rules for "unique biological material" "*obtained from nature*" should not apply to "novel *genetically-engineered* biological subject matter." (A19, A20) (emphasis added). With respect to the latter, the court held, no sample need be deposited: a written description of the recombinant DNA techniques used to create the organism in the laboratory is sufficient to meet the best mode requirement, even if that description does not enable others to "duplicate" or "reproduc[e]" the inventor's contemplated best mode cells. (A22, A23). So long as others can *eventually* produce *something like* the best mode cells, the law is satisfied.

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[3] The potency or purity of EPO is stated as its specific activity, expressed as a ratio of International Units (IU) per absorption unit (AU). (A31 n.10).

The Federal Circuit did not question the district court's finding of concealment by Lin in his "failure to deposit the transfected cells notwithstanding the fact that he was willing to deposit essentially worthless cell material." (A23). It simply held that, in a case involving genetically engineered microorganisms where written directions for making something like the best mode have been provided, evidence of deliberate concealment becomes "irrelevant" as a matter of law. (A23).

The Federal Circuit also held that, even if Amgen *had* violated the best mode requirement of the statute, only its host cell claims would be invalid, and Amgen would still be allowed in that event to retain its patent monopoly on the isolated DNA sequence and vectors used to create EPO cell factories, even though it may have violated 35 U.S.C. § 112 by attempting to retain as a trade secret the best mode of practicing its invention. (A17 n.5).

Finally, the Federal Circuit reversed the district court, which had held that Amgen failed to prove that GI's purified hormone patent was not enabled. (A32). The court of appeals did not deem the district court's findings (which dismissed Amgen's evidence) to be clearly erroneous. Instead, the Federal Circuit (1) sidestepped that traditional appellate role by belatedly shifting the burden of proof to GI, holding, *after* the trial was over, that GI should have proved that its own patent was enabled (A32, A34); and (2) subverted the rule against appellate fact-finding by going behind the district court's findings of fact to make its own, contrary findings as to the specific evidence Amgen had submitted. (A32-A34).

REASONS FOR GRANTING THE WRIT

I. The Federal Circuit's Distinction Between Genetically Engineered Life Forms And All Other Inventions Contravenes The Patent Laws Enacted By Congress, Exceeds The Institutional Limits On The Judiciary Affirmed In *Diamond* v. *Chakrabarty*, And Undermines The Constitutional Policy Of Promoting The "Progress Of Science And The Useful Arts."

The biotechnology industry has quite plainly gotten the message from the decision below that genetic engineers need not make the choice between trade secrets and patent protection that the law imposes on all other inventors:

> [I]f you have a biotechnology invention involving a product that is made through use of a proprietary bioculture, you can get a patent on the product and keep your proprietary bioculture a secret. . . . [The Federal Circuit's holding is] an invitation to patent genetic engineering inventions "in a way that will allow patent holders to protect their cell lines." The advice is already being given that "[a]s of now, companies don't have to deposit their best cell lines, meaning that they can keep them as trade secrets."

Halluin & Wegner, *Biotechnology Practice After Amgen* and *Scripps*, American Intellectual Property Law Ass'n Biotechnology Litigation Report at 16 (March 1991).

If uncorrected, the legacy of the judgment below would be both cruelly ironic and devastating to the progress of genetic engineering. For in *Chakrabarty* itself, the American Society for Microbiology successfully urged this Court to reject a distinction between compositions of matter occurring in nature and those produced in the laboratory by artificial means, precisely because inventors of artificial life forms, if denied patent

protection, would refuse to deposit their cell lines and thereby stultify research and advancement in genetic engineering. Brief Amicus Curiae in *Diamond* v. *Chakrabarty*, No. 79-136 at 10-11. The decision below incurs these very consequences while awarding patent protection!

Now is the time for the Court to consider this issue, while the commercialization of genetically engineered life forms is still aborning. For as long as the decision below remains in force, genetic engineering patents will be filed without deposits of the best mode cell lines, and both the public and the "Progress of the useful Arts" will be shortchanged on the bargain Congress struck in 35 U.S.C. § 112.

A. 35 U.S.C. § 112 Requires All Patentees To Give Up Trade Secret Protection On The Best Mode Of Their Inventions.

American patent law embodies a contract between society and the inventor: in exchange for full disclosure of the invention that will advance the "Progress of Science and the useful Arts," Art. I, § 8, cl. 8, the inventor receives a 17-year monopoly on commercial use of his discovery. *See Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 109 S.Ct. 971, 975 (1989); *Kewanee Oil Co.* v. *Bicron Corp.*, 416 U.S. 470, 480-81 (1974). Thus the inventor must choose between retaining his invention as a trade secret or putting it in the public's hands and receiving a patent. "As Judge Learned Hand once put it: . . . 'he must content himself with either secrecy or legal monopoly.'" *Bonito Boats*, 109 S.Ct. at 977.

Consequently, Congress has required not only that the patent specification describe the invention in such terms "as to *enable* any person skilled in the art . . . to make and use" some form of it, but also that the specification "set forth the *best mode* contemplated by the inventor of carrying out his invention." 35 U.S.C. § 112 (emphasis added). *See Dana Corp.* v. *IPC Ltd. Partnership*, 860 F.2d 415, 418 (Fed.Cir. 1988), *cert.*

denied, 490 U.S. 1067 (1989). The goal is to allow others who wish to experiment with and improve upon the invention during the patent's term, or to use it thereafter, to start where the original inventor left off — without, in essence, having to reinvent the wheel. *See Kewanee Oil*, 416 U.S at 480-81. Since 1793, Congress accordingly has made clear that attempts to conceal information from the public — whether or not such concealment makes it unduly difficult to use the invention — invalidate the patent.[4] This history demonstrates that at the core of the "best mode" requirement of the present § 112 is a long-standing condemnation, rooted in the Constitution's Patent Clause itself, of any scheme to conceal, for commercial gain, relevant information about how best to make an invention into a reality.

B. Congress' Best Mode Requirement Makes No Distinction Between Natural And Genetically Engineered Life Forms And The Federal Circuit Has No Authority To Enact Such A Distinction.

Nothing in 35 U.S.C. § 112 supports a distinction between microorganisms first created by genetic engineering and those already found in nature. Indeed, in another context the Federal Circuit itself has held that "there is nothing unique" about

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[4] Section 6 of the original patent act of 1790 provided a defense to what would now be brought as a suit for infringement if the inventor's specification "does not contain the *whole of the truth* concerning his invention." Act of April 10, 1790, ch. 7, § 6, 1 Stat. 109 (emphasis added). The 1793 Act modified this "whole truth" defense to make it clear that this required more than mere enablement of the invention. Act of Feb. 21, 1793, ch. 11, § 6, 1 Stat. 318. Furthermore, an inventor's failure to disclose the "several modes" for practicing his invention was enough to defeat an action for infringement. *See id.* at § 3. The 1870 Act commanded the inventor of a machine to reveal "the best mode in which he has contemplated applying" his invention. Act of July 8, 1870, ch. 230, § 26, 16 Stat. 198. The "whole truth" provision was retained as a defense. Finally, the 1952 Act extended this "best mode" language to cover *all* inventions, not just machines. Act of July 19, 1952, ch. 950, § 1, 66 Stat. 798. The 1952 Act eliminated the "whole truth" defense as a separate provision; it was subsumed by the "best mode" requirement.

Amgen's host cell patent, *Amgen Inc.* v. *U.S. Int'l Trade Comm'n*, 902 F.2d 1532, 1538 (Fed.Cir. 1990), nor "any difference between Amgen's host cell product claims and any other product claim which would merit giving the host cell claims special treatment" for the purpose of the patent law provisions of the Trade Act of 1988. *Id.* at 1537.

When the Court of Customs and Patent Appeals first confronted the issue of biological deposits under § 112 in 1970 in *Application of Argoudelis*, 434 F.2d 1390 (C.C.P.A. 1970), it was urged to relax the statutory requirement for microorganisms as Congress had done for asexually produced plants. The court properly declined:

> In regard to plants, a general dispensation from the requirements of § 112 has been accorded by 35 U.S.C. § 162. It is urged that the same should be true here. *We do not believe that a general dispensation from the statutory requirements of § 112 in the case of microorganisms is necessary, desirable, or within the province of this court to grant.* Our task here is not to decide what the general rule should be or to create exceptions to the provisions of § 112, but rather to interpret and apply § 112 to the facts of the case before us.

434 F.2d at 1392 (emphasis added). A decade later, that same court was asked in *Chakrabarty* to treat genetically engineered bacteria as legally distinct from other "composition[s] of matter" and hence as unpatentable under 35 U.S.C. § 101. Once again, it declined. This Court affirmed that decision, noting that "Congress is free to amend § 101 so as to exclude from patent protection organisms produced by genetic engineering. . . . But until Congress takes such action, this Court must construe the language of § 101 as it is." 447 U.S. at 318.

This time, however, the court below — perhaps mesmerized by the marvels of new technology — has succumbed to the pleas for a judge-made dispensation from the patent law regime

that Congress enacted for all inventions, and therein lies reason for this Court to grant a writ of certiorari. Just as Congress decreed that *all* "composition[s] of matter" may be patented when it enacted 35 U.S.C. § 101, *Chakrabarty*, 447 U.S. at 315, 318, so it decreed — when it amended § 112's predecessor provision in 1952 to require explicitly that the "best mode" be set forth for *all* inventions, not just for machines — that the best embodiment of an invention be placed in the public's hands *regardless of the particular technology involved*. *See* note 4, *supra*. Just as, pursuant to § 114 (see page 19, *infra*), deposits of naturally occurring antibiotic-producing bacteria have been required to comply with § 112, so too deposits of genetically engineered hormone-producing mammalian cells should be required unless and until Congress or the appropriate policy-making agency decides otherwise.

C. The Decision Below Effectively Exempted Genetically Engineered Life Forms From The Best Mode Requirement By Upholding Respondent's Refusal To Deposit Its Cell Line.

Under 35 U.S.C. § 112, the patentee's best mode must "be fully, clearly, and precisely disclosed if the public is to receive the benefits intended to result from the grant of the patent monopoly." *Union Carbide Corp.* v. *Borg-Warner Corp.*, 550 F.2d 355, 360 (6th Cir. 1977). The disclosure is insufficient unless others skilled in the art can *reproduce* the patentee's contemplated best mode. With respect to patents involving microorganisms, the standard even for mere enablement, let alone the disclosure of the best mode, has long been held to require such *reproducibility*, and that in turn has mandated public deposits of samples of the microorganisms. This is confirmed by the Federal Circuit's own authorities. (A19).[5]

[5] *See In re Lundak*, 773 F.2d 1216, 1219 (Fed.Cir. 1985) ("Because of the uncertainties of *reproducibility* that inhere in such processes [of mutagenesis and isolating a new human cell line], at least in the present state of biotechnology, this invention is of the class covered by the deposit requirement.") (em-

It is undisputed that, because of the randomness and unpredictability inherent in the genetic engineering process, Amgen's best mode CHO cell line could not be reproduced without access to a deposit of that cell line. The district court found that "no scientist could ever duplicate exactly the best mode used by Amgen" (A22), and the court of appeals accepted that "the record shows that scientists were unable to duplicate Lin's genetically-heterogenous best mode cell strain." (A22).

To dispose of this awkward fact, the court below simply distinguished patents involving naturally occurring organisms from those involving novel genetically engineered organisms and made up a new, lower standard for disclosure of the best mode with respect to the latter.[6] The new rule is that genetic engineers need not, as § 112 mandates, actually "set forth the best mode" of their inventions: they need only provide a rough map of how to *hunt for something like the best mode*, and a sketch of what one may expect to find if one ever stumbles upon it. Indeed, the sketch need not even be good enough to enable the map-follower to recognize when the goal has been *reached*! For Amgen was not required to provide even the level of specification deemed inadequate in the cases listed in note 5, *supra* (*see also* note 10, *infra*), inasmuch as its oblique reference to its best mode CHO cells referred only to their

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phasis added); *Application of Argoudelis*, 434 F.2d 1390, 1391 (C.C.P.A. 1970) ("the invention [producing antibiotics from a microbe] can be *reproduced* without experimentation by one of ordinary skill" only because the producing microbe has been deposited) (emphasis added).

[6] The court below made no attempt to distinguish the cases discussed in note 5, *supra*, on this issue of reproducibility. It simply asserted that § 112 does not require that the best mode be "precisely and universally reproducible." (A23). The only authority cited for this proposition was *In re Gay*, 309 F.2d 769 (C.C.P.A. 1962). But that case held only that a patent specification need not describe every conceivable, non-crucial detail of a particular commercial application, "else patent specifications would turn into production specifications, which they were never intended to be." *Id.* at 774. *Gay* is wholly inapposite, for petitioners demand disclosure (through a deposit) only of Amgen's best mode cell line — *not* of Amgen's commercial mass production techniques, such as the specifications for its cell vats. Indeed, Amgen itself probably did not know those production details at the time it filed its last patent application, and petitioners and the public are entitled to (and ask for) only the best mode that Amgen contemplated at that time.

EPO production level, omitting any clue as to the other vital cell characteristics that Amgen indisputably weighed in choosing its best mode cell line.[7] Although such cell attributes must have been the determining factor, since Amgen did *not* select the line that produced the greatest amount of EPO (A129), one can only guess at the trade-offs made among these diverse characteristics because Amgen neither disclosed them in its patent nor deposited a sample for others to inspect.

The Federal Circuit's open acceptance of a lower best mode disclosure standard for genetically engineered organisms is dramatized by its reliance on the testimony of GI's expert witness, Dr. Simonsen. As the court notes, Dr. Simonsen testified that by using the DNA sequence and vectors set forth in Example 10 of Amgen's genetic engineering patent (*see* Appendix F), "someone could *eventually* reproduce — well, could generate cell lines making *some level* of EPO, and they could be better, *they could be worse* in terms of EPO production." (A20) (emphasis added). By definition that is a second-best or "worse" mode, rather than the best one, and "the 'best mode' requirement does not permit an inventor to disclose only what he knows to be his second-best embodiment, retaining the best for himself." *Application of Nelson*, 280 F.2d 172, 184 (C.C.P.A. 1960).

1. The Rationale for the Federal Circuit's Judge-Made "No Deposit" Rule for Artificial Life Forms Is Deeply Flawed.

The court below sought to distinguish the long line of patent cases involving naturally occurring microbes used to produce antibiotics, in which cell deposits were required, on the ground that naturally occurring microorganisms might be rare in nature

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[7] Amgen's own witnesses testified that they considered such factors as cell stability, growth rates, durability in culture, freezing and thawing, and the potency and therapeutic suitability (as opposed to the mere quantity) of the EPO produced. (Fed.Cir.App. at 27,192; 35,628) (Deposition of Amgen employee Dr. Jeffrey Browne at 50, 51, 59).

and hard to find, whereas "when . . . the organism is created by insertion of genetic material into a cell obtained from generally available sources," those wishing to use or experiment with the best mode can simply assemble their own host cells in the laboratory by following the instructions on genetic engineering laid out in the patent. (A20-A21). Thus unique new cell lines, created in a laboratory by human hands under experimental conditions and incapable of ever being exactly reproduced, were paradoxically deemed *more common and more accessible* to the public than naturally occurring organisms found in soil samples and mold cultures.

There are at least two fundamental flaws in this judicially legislated rule for genetic engineering patents. *First*, the court below held that deposits are unnecessary for genetically engineered cell lines because, in contrast to the antibiotic cases, the "starting materials" necessary to practice the best mode of a patent like this are "publicly available" — mammalian cells can be obtained in the scientific community and transfected with the human EPO gene according to the instructions in Example 10 to create some sort of host cell to produce the EPO hormone. (A20-A21). But the "starting materials" that had to be deposited (because they were deemed rare and not publicly available) in the antibiotic cases upon which the Federal Circuit relies were *not* the original soil samples from which the microbes might eventually be cultured, refined and isolated; *they were the antibiotic-producing microbes themselves. See In re Lundak*, 773 F.2d 1216, 1217-18 (Fed.Cir. 1985); *Feldman* v. *Aunstrup*, 517 F.2d 1351, 1352, 1355 (C.C.P.A. 1975), *cert. denied*, 424 U.S. 912 (1976); *Application of Argoudelis*, 434 F.2d 1390, 1390-91, 1392 (C.C.P.A. 1970).

The application of that well-established deposit requirement here would mandate that Amgen deposit the EPO-producing transfected CHO host cells themselves in order to meet the best mode requirement. The court below avoided that obvious result not by logic but by brute force: it simply rewrote the deposit rule implementing 35 U.S.C. §§ 112 and 114, and in

effect revised § 112 itself, to require that the public be assured ready access not to the best mode cell line that the inventor *ended up* with at the time he applied for his patent, as Congress mandated, but to the unexceptional raw materials that the inventor himself had *started* with years before.[8]

Second, the only arguable excuse for the court of appeals' conclusion that organisms created by genetic engineering from a mammal's cells are readily available to any scientist skilled in the art and hence need not be deposited would be the blithe assumption, in the face of the Federal Circuit's own contrary findings (A12, A22), that recreating a specific, novel mammalian cell line is a simple, predictable and straightforward matter of following written instructions — rather like assembling a bunch of Lego blocks according to the directions on the back of the toy box. (A20-A21). Nothing could be further from the truth — or could better illustrate the folly of judicial legislation in this field. As the Patent Office itself has repeatedly recognized, "experiments in genetic engineering produce, at best, unpredictable results." *Ex parte Forman*, 230 USPQ 546, 458 (PTO Bd. of Pat. App. and Interferences 1986). Even with respect to simple bacterial cells, which are far less complicated and challenging subjects than the mammalian cells needed to produce EPO, genetic engineering is a hit-or-miss proposition:

> One skilled in this art, as clever and innovative as he may be, cannot find or produce, on demand, the organisms necessary for use in the claimed [antibiotic] process. Even considering the newly developing biological engineering techniques, at this time it is

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[8] The microbes for which a deposit was required in the case on which the Federal Circuit relies (A21) were not of obscure or exotic origin: the soil sample in which they were found had been taken from the inventor's backyard compost heap. *Feldman*, 517 F.2d at 1352. *See also Ex parte Kropp*, 143 USPQ 148, 149 (Pat. Off. Bd. of App. 1959) (microbes found in soil sample from Pennsylvania farm). Yet a deposit was required so that others wishing to improve upon the invention (or to practice it once the patent expired) would not have to start over where the patentee began.

> just not feasible to expect one skilled in the art to "manufacture" the necessary microbe.

Ex parte Jackson, 217 USPQ 804, 809 (PTO Bd. of App. 1982).[9] To say that scientists provided with the written description in Example 10 could "*eventually*" produce something akin to Amgen's best mode host cells reveals only a mundane truth about the laws of probability: after all, if you provide enough chimpanzees with typewriters, they will "eventually" produce something like *Hamlet*.

The uncertainty even of the far simpler scientific processes involved in culturing and isolating naturally occurring microorganisms has consistently led the courts to hold that patent specifications that provide a taxonomic description of a microorganism, list its desired characteristics, and give instructions on how to obtain it are nevertheless inadequate under § 112 unless accompanied by a deposit of the microorganism itself.[10] This is precisely why scientists and organizations such as the American Society of Microbiology have argued that "a written description of a novel microorganism in a patent specification is of little aid to other scientists if that microorganism is not available through a public depository." I. Cooper, *Biotechnol-*

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[9] When Chinese hamster ovary or other mammalian host cells are exposed to identical plasmids containing the human EPO gene, millions of unique, genetically varied cell types result, some with the gene, some without, some with more than one copy of it. (A56-A57). This transfection may affect thousands of operations within the host cell in unpredictable ways, because the gene may insinuate itself into the host cell's nucleus at any of a multitude of different locations along the DNA chain that runs as a vast, convoluted thread through the entire assembly. That DNA chain is the source of all decisions and changes of direction in the cell's existence. Moreover, where the EPO gene randomly locates itself is the single most critical factor in determining how the gene amplification process proceeds. That process, which is necessary to produce a stable subpopulation of transfected cells with desired characteristics, is entirely random at each and every one of its many steps or iterations. Despite the most detailed specification of these steps, there is no way to control or predict its outcome for any particular cell or set of cell characteristics.

[10] *See In re Lundak*, 773 F.2d at 1220; *Feldman*, 517 F.2d at 1352; *Argoudelis*, 434 F.2d at 1392; *Ex parte Kropp*, 143 USPQ at 152.

ogy and the Law § 1.02 (1991). For this reason, too, scientific journals such as *Virology* require authors of prospective articles to make the cell strains, plasmids, vectors and viruses described in their articles "freely available for distribution upon request" to all members of the scientific community. *Virology*, July 1991, at vii.

Although the public is entitled, with respect to chemical compounds, mechanical or electrical inventions, and naturally occurring organisms, to access to "the preferred embodiment of the invention," *Dana Corp.*, 860 F.2d at 418 — and although nothing is more literally an "embodiment" of an invention in microbiology than the cells themselves — the court below flouted § 112 by holding that, when it comes to genetically engineered organisms, the inventor need not provide access to the actual embodiment of his invention and may instead put the public to the futile task of *hunting for it*.

2. The Federal Circuit Confused the Best Mode and Enablement Requirements of the Statute.

Section 112's "enablement" and "best mode" requirements are separate and distinct; a patent specification might enable one skilled in the art to practice the invention in some form without revealing what the inventor knows to be the best mode for doing so. *See Spectra-Physics, Inc.* v. *Coherent, Inc.*, 827 F.2d 1524, 1537 (Fed.Cir.), *cert. denied*, 484 U.S. 954 (1987); *In re Gay*, 309 F.2d 769, 772 (C.C.P.A. 1962). That the decision below confuses the best mode and enablement requirements of § 112 is apparent from the language of the Federal Circuit's opinion: the court of appeals reasons that no deposit is required because "the best mode cells have been *enabled*." (A21) (emphasis added). (*See also* A20) ("the best mode was . . . adequately enabled."). This "enablement" exists, we are told, because transfected CHO cells can supposedly "be prepared without undue experimentation" by one "skilled in the art from known materials using the description in the specification," and then cells *similar* to Amgen's best mode — " 'mak-

ing some level of EPO, they could be better, *they could be worse*'" — may be selected. (A20) (emphasis added). But this simply does not speak to the *best mode* issue.

The flaw in the decision below is systemic in its implications. For the Federal Circuit has held that, although best mode and enablement are separate requirements under 35 U.S.C. § 112 in every other field of patent law, the best mode requirement is subsumed by (and satisfied by) simple enablement when it comes to genetic engineering.[11] Thus the decision below has rewritten § 112 to short-change the public in the patent bargains it strikes with inventors in the one area — biotechnology — that is perhaps the most active and growing field of scientific endeavor today and that holds the greatest promise for solving the pressing health and medical problems our world confronts.

D. The Federal Circuit Diluted Congressional Condemnation Of An Inventor's Concealment Of His Best Mode.

Applicants wishing to avail themselves of patent monopolies must maintain "the highest degree of candor and good faith. . . . [The Patent] Office . . . must rely upon their integrity and deal with them in a spirit of trust and confidence." *Kingsland* v. *Dorsey*, 338 U.S. 318, 319 (1949). Because of the far-reaching social and economic consequences of a patent, the definition of "concealment" of the best mode by a patent applicant is expansive.[12] And the district court expressly found

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[11] Conflation of the best mode and enablement requirements has been consistently rejected outside the field of genetic engineering. *See, e.g., Union Carbide* v. *Borg-Warner*, 550 F.2d at 361 ("It could be argued that one of ordinary skill in the plastics molding art would be able, without undue experimentation, to select an extruder that would work. This would satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. However, the question here involves the best mode requirement, and [the inventor's] own testimony shows that some extruders do a better job than others.").

[12] Conduct need not "rise to the level of active concealment or grossly inequitable conduct in order to warrant invalidation of a patent," *Union Carbide* v. *Borg-Warner*, 550 F.2d at 363, for although "[u]nintentional obtuseness or

evidence of concealment of the best mode in this case because Amgen deposited only worthless bacterial cells. (A128-A129, A130-A131). When the patent specification was initially rejected because of the Patent Examiner's doubts about the adequacy of the deposit (A131), Amgen reassured the Examiner that appropriate cell deposits would be maintained. But the Examiner could not be expected to know what Amgen did not disclose — that the bacterial cells Amgen deposited did not embody the best mode of its invention, because EPO generated by bacteria is inactive in the human body and therefore of no value whatsoever to a human patient. Amgen was under a duty to disclose the nature and value (or lack thereof) of its cell deposits to the Patent Examiner, even if the Examiner had not expressed a particular interest in the deposit issue.[13] The Federal Circuit did not question the conclusion, reached by the district court, that "Lin's failure to deposit the transfected cells notwithstanding the fact that he was willing to deposit essentially worthless cell material was evidence of deliberate concealment." (A23).[14] Instead, the circuit court, obviously

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obfuscation might be a reason not to penalize someone; [it is not] a reason for granting a 17-year monopoly." *Dale Electronics* v. *R.C.L. Electronics*, 488 F.2d 382, 389 (1st Cir. 1973).

[13] *See Chas. Pfizer & Co., Inc.* v. *FTC*, 401 F.2d 574, 583-87 (6th Cir. 1968) (inventor required to grant licenses and provide its own microbe culture on demand to one and all because patent examiner was misled when inventor failed to disclose deficiencies in fermentation process that it should have known examiner would be interested in after having once rejected the application); *cert. denied*, 394 U.S. 920 (1969); *Consolidated Aluminum Corp.* v. *Foseco Int'l Ltd.*, 910 F.2d 804, 807-09 (Fed.Cir. 1990) (patent unenforceable because inventor disclosed not his best mode ceramic foam composition but a different composition incapable of producing the invention's desired result).

[14] The court below agreed that the Examiner initially rejected the patent application "for failure to make a publicly accessible biological deposit," but it discounted this fact because, supposedly, "that rejection was withdrawn after an oral interview and a written argument that the invention did not require a deposit." (A21). *The Federal Circuit is flatly mistaken.* Its own citations to the patent prosecution history reveal that, although Amgen objected at one point that its invention did not depend upon specific plasmids or cells, it nevertheless hastened to reassure the patent examiner that appropriate deposits had been made and would be maintained as necessary. *See* pages 6-7, *supra*.

confronted with a game of hide-and-seek, once again engrafted a special exception onto § 112 for genetic engineering patents, holding that concealment of the best mode is "irrelevant" *as a matter of law* when something like the best mode cells has been "enabled" by a written description. (A23).

E. The Federal Circuit's Rejection Of The Usual Remedy Of Patent Invalidation In This Setting Will Prove To Be Particularly Pernicious In The Field Of Genetic Engineering.

The court of appeals recognized that the invention set forth in Amgen's genetic engineering patent encompassed the isolated DNA sequence for EPO, the vectors used to transfect that gene into another cell, and the transfected EPO-producing host cells themselves. (A5). Yet the court ruled that, even if it were found that Amgen had violated the best mode requirement for this invention, *only* its host cell claims would be invalidated: Amgen would retain its patent monopoly on the isolated DNA sequence and vectors used to make those host cells. (A17 n.5). The Federal Circuit appears once again to have carved out an arbitrary and unwarranted patent law exception for genetically engineered biological material.[15]

Only then was the Examiner's objection withdrawn, and Amgen in fact made further deposits (albeit deposits the Federal Circuit itself characterized as "essentially worthless," A23). Indeed, far from challenging the deposit requirement, Amgen proceeded to rely on its deposits in answering some of the Patent Examiner's other objections, contending that, in "U.S. Patents relating to inventions in biotechnology, it has been found appropriate to identify novel microorganisms and cell lines in the claims through reference to a deposit." Prosecution History at 213 (Oct. 2, 1986) (Fed.Cir.App. 26,043).

[15] When the best mode that is concealed is not merely the preferred form of carrying out a few discrete claims, but the best mode of practicing the entire patented invention, a violation of the best mode requirement invalidates the entire patent. *See, e.g., Chemcast Corp.* v. *Arco Industries Corp.*, 913 F.2d 923 (1990)); *Dana Corp.* v. *IPC Ltd. Partnership*, 860 F.2d 415 (Fed.Cir. 1988); *Spectra-Physics, Inc.* v. *Coherent, Inc.*, 827 F.2d 1524 (Fed.Cir. 1987). The court below never even cited this body of precedent, relying exclusively on *Northern Telecom, Inc.* v. *Datapoint Corp.*, 908 F.2d 931, 940 (Fed.Cir.), *cert. denied*, 111 S.Ct. 296 (1990). (A17 n.5). *Northern Telecom* affirmed a

Invalidating Amgen's genetic engineering patent on less than the entire invention makes no sense. The transfected CHO host cells are not merely the "best mode" of practicing Amgen's host cell *claims*, as the Federal Circuit seems to believe; they are the best mode "of carrying out," 35 U.S.C. § 112, the genetic engineering patent's *invention* for producing EPO by recombinant DNA technology. To give the public only the "right" to possess or use transfected host cells without obtaining a license from Amgen, as a sanction for Amgen's concealment, *is to give the public — and to withhold from Amgen — absolutely nothing*, since it is impossible for anyone to create transfected host cells without using and reproducing the isolated DNA sequence on which Amgen would retain a patent monopoly. Amgen's genetic engineering patent cannot be disaggregated after the fact and upheld piecemeal in the face of Amgen's concealment of "the 'best mode' known at the time to [it] of making and using the invention." *SRI Int'l* v. *Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1121 (Fed.Cir. 1985). The truncated "invention" that the Federal Circuit would sustain, represented by the isolated EPO gene and the vectors for transfecting it, simply cannot be "made or used" without the creation of host cells. Indeed, virtually the only use — and certainly the overwhelmingly important use — for the isolated DNA sequence and the vectors is the creation of host cells to produce EPO. If this salami-slicing approach is allowed to stand, then the promise of full disclosure to the public in exchange for the inventor's patent monopoly will have become "a promise to the ear to be broken to the hope, a teasing illusion like a munificent bequest in a pauper's will." *Edwards* v. *California*, 314 U.S. 160, 186 (1941) (Jackson, J., concurring).

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district court decision invalidating certain patent claims on best mode grounds. Neither the district court opinion nor that of the court of appeals in *Northern Telecom* even noted the fact that the entire patent had not been ruled invalid, much less addressed the issue.

II. The Federal Circuit's Shifting Of The Burden Of Proof To The Patent-Holder, And Its Substitution Of Its Own Factual Findings On GI's Patent For Those Of The District Court, Violate 35 U.S.C. § 282 And Conflict With *Anderson* v. *City of Bessemer* and Fed.R.Civ.P. 52(a).

Section 282 of Title 35 places the burden of proving that a patent claim has not been enabled squarely on the party challenging the patent. Appendix G (A240). *See Ralston Purina Co.* v. *Far-Mar-Co., Inc.*, 772 F.2d 1570, 1574 (Fed.Cir. 1985). Although the Federal Circuit paid lip service to this statute (A34), it openly flouted it in holding that claims 1 and 3 of GI's purified hormone patent had not been enabled: "Defendant[ ] [GI] ha[s] produced no evidence that it ever prepared EPO with a specific activity of at least 160,000 IU/AU *in vivo* using the disclosed methods." (A32). The Federal Circuit reasoned that "Amgen has met its burden to show that the claims have not been adequately enabled" *not* because of evidence offered by Amgen itself, but because *GI* supposedly adduced "no *credible* evidence that the claimed purified material can be made by those skilled in the art by the disclosed process." (A34) (emphasis added).[16]

The court of appeals then proceeded to brush aside the district court's findings of fact and to consider the trial evidence and the credibility of witnesses and documents for itself, in violation of Fed.R.Civ.P. 52(a). Appendix G (A241). The district court had expressly found that every piece of evidence of non-enablement offered by Amgen was meaningless because there was *nothing* to indicate that the EPO purification attempts

[16] At another point the Federal Circuit held that the district court "erred in finding enablement" because the evidence GI presented about Dr. Kung's successful efforts using GI's process supposedly "does not demonstrate enablement of the claimed invention." (A33). The court of appeals itself recognized that it was departing from § 282 by reversing the statutory presumption of patent validity in this case: "We do not hold that one must *always* prove that a disclosed process operates effectively to produce a claimed product." (A34) (emphasis added).

described in Amgen's evidence had in fact used the process disclosed in GI's purified hormone patent. (A185-A186). And the district court had credited "strong . . . evidence" presented by GI, which "Amgen never addressed," that other scientists had successfully used the process disclosed by GI. (A186).

The court of appeals did not deem these findings clearly erroneous, it simply ignored them. For example, the Federal Circuit found that GI's own submission to the FDA proves that its patent was not enabled: a particular EPO sample GI described to the FDA did not meet the patent's standard of purity even though, according to the court of appeals, it was supposedly processed by the "technique taught by [GI's purified hormone] patent." (A32). This flies in the face of the district court's finding that "Amgen has provided *no evidence* to indicate that those samples were prepared by the [procedures disclosed in GI's patent] or their equivalent" (A186).[17]

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[17] The primary evidence relied upon by the Federal Circuit to prove non-enablement was an Investigational New Drug Application (IND) submitted to the FDA by GI and Chugai, in which GI supposedly "stated that it had purified EPO material 'to homogeneity' by subjecting partially purified EPO material to . . . the technique taught by Hewick in the [purified hormone] patent." (A32). Since the IND stated that the purity of this particular sample of EPO was assayed at only 109,000 IU/AU, well short of the 160,000 figure claimed in GI's patent, the Federal Circuit concluded that GI's own FDA submission proved that its patent was not enabled. (A31-A33).

This conclusion reverses the district court's findings and flatly contradicts the record. *First*, the district court found that there was *no evidence* that the FDA sample had been prepared by GI's process. (A186). (*See also* Fed.Cir.App. at 19,211-217). *Second*, the record before the district court indicated that the sample referred to in the IND was assayed *before* it was ever subjected to GI's advanced purification process — hence the low assay figure. *See* Fed.Cir.App. at 22,186; 9,586-9,950. *Third*, the IND sample proves absolutely nothing about enablement, because GI and Chugai did *not* claim that the sample had, at the time it was assayed at 109,000, been "purified to homogeneity" in accord with the patent as the Federal Circuit seemed to believe. (A32). The documents submitted to the FDA (which the Federal Circuit quotes without citation, A32) described the sample at *that* stage, *before* application of the advanced purification process disclosed by GI, as merely being "highly purified." (Fed.Cir.App. at 22,186). The term "purified to homogeneity," a term of art under GI's patent, was used in the documents to describe the EPO sample only *after* it had been further refined, and *no* assay was performed on the sample at that stage. (*Id.* at 22,081).

This Court has chastised appellate courts for just such usurpation of the trial court's role: "The standard [of Rule 52(a)] plainly does not entitle a reviewing court to reverse the finding of the trier of fact simply because it is convinced that it would have decided the case differently." *Anderson* v. *City of Bessemer*, 470 U.S. 564, 573 (1985). *See also Panduit Corp.* v. *Dennison Mfg. Co.*, 810 F.2d 1561, 1565 n.3 (Fed.Cir.) ("That a question is legal does not, of course, free an appellate court to ignore Rule 52(a), to disregard the clearly erroneous standard, to make its own findings *de novo*, or simply to disagree on whim with the district court's legal conclusion"), *cert. denied*, 481 U.S. 1052 (1987). Since patent cases often involve difficult and unfamiliar factual inquiries, a grant of review on the first question would offer a useful opportunity to ensure, by granting review on the second question as well, that the Federal Circuit is complying with Rule 52(a) and *Anderson* in discharging its unique appellate role in this area of law.

CONCLUSION

Not content to usurp the policy-making role of Congress and the Patent Office with respect to the best mode requirement for genetic engineering patents in order to uphold Amgen's patent, the Federal Circuit also arrogated to itself the fact-finding role of the district court with respect to enablement in order to invalidate GI's purified hormone patent. In these two independent respects, the Federal Circuit has profoundly mis-

conceived its place in protecting the "Progress of Science and the useful Arts." A writ of certiorari should therefore be granted.

Respectfully submitted,

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TABLE OF CONTENTS

APPENDIX A

Opinion of the United States Court of Appeals for the Federal Circuit, dated March 5, 1991 . . . . A1

APPENDIX B

Memorandum and Order of the United States District Court for the District of Massachusetts (Saris, U.S.M.), dated December 11, 1989 (As Corrected January 30, 1990) A39

APPENDIX C

Memorandum and Order of the United States District Court for the District of Massachusetts (Young, J.), dated January 31, 1989 . . . . . A193

APPENDIX D

Judgment of the United States District Court for the District of Massachusetts (Young, J.), dated March 14, 1990 . . . . . A228

APPENDIX E

Order of the United States Court of Appeals for the Federal Circuit denying rehearing, dated April 2, 1991 . . . . . A231

APPENDIX F

Example 10 from Amgen's U.S. Patent 4,703,008 A232

APPENDIX G

Text of constitutional and statutory provisions and rule involved A240

APPENDIX A

United States Court of Appeals for the Federal Circuit

90-1273,-1275

AMGEN, INC.,

Plaintiff/Cross-Appellant,

v.

CHUGAI PHARMACEUTICAL CO., LTD., and GENETICS INSTITUTE, INC.,

Defendants-Appellants.

Edward M. O'Toole, Marshall, O'Toole, Gerstein, Murray & Bicknall, of Chicago, Illinois, argued for plaintiff/cross-appellant. With him on the brief were *Michael F. Borun, Richard A. Schnurr* and *Christine A. Dudzik*. Also on the brief were *Steven M. Odre* and *Robert D. Weist*, Amgen, Inc., of Thousand Oaks, California, of counsel.

Kurt E. Richter, Morgan & Finnegan, of New York, New York, and *William F. Lee*, Hale & Dorr, of Boston, Massachusetts, argued for defendants-appellants. Of Counsel were *Eugene Moroz, Michael P. Dougherty* and *William S. Feiler*, Morgan & Finnegan, of New York, New York.

Appealed from: U.S. District Court for the District of Massachusetts

Judge Young

United States Court of Appeals for the Federal Circuit

90-1273,-1275

AMGEN, INC.,

Plaintiff/Cross-Appellant,

v.

CHUGAI PHARMACEUTICAL CO., LTD., and GENETICS INSTITUTE, INC.,

Defendants-Appellants.

DECIDED: March 5, 1991

Before MARKEY, LOURIE, and CLEVENGER, *Circuit Judges*. LOURIE, *Circuit Judge*.

This appeal and cross appeal are from the March 4, 1990, judgment of the United States District Court for the District of Massachusetts, No. 87-2617-Y, *Amgen, Inc.* v. *Chugai Pharmaceutical Co.*, 13 USPQ2d 1737 (1990), and involve issues of patent validity, infringement, and inequitable conduct with respect to two patents: U.S. Patent 4,703,008 ('008), owed by Kirin-Amgen Inc. (Amgen), and U.S. Patent 4,677,195 ('195), owned by Genetics Institute, Inc. (GI).

Chugai Pharmaceutical Co., Ltd. (Chugai) and Genetics Institute, Inc. (collectively defendants) assert on appeal that the district court erred in holding that: 1) Amgen's '008 patent is not invalid under 35 U.S.C. §§ 102(g) and 103; 2) the '008 patent is enforceable; 3) the failure of Amgen to deposit the best

mode host cells was not a violation of the best mode requirement under 35 U.S.C. § 112; and 4) claims 4 and 6 of GI's '195 patent are invalid for indefiniteness under 35 U.S.C. § 112.

On cross appeal, Amgen challenges the district court's holdings that: 1) claims 1 and 3 of the '195 patent are enabled; 2) the '195 patent is enforceable; 3) this is not an exceptional case warranting an award of attorney fees to Amgen; and 4) claims 7, 8, 23-27 and 29 of the '008 patent are not enabled by the specification.

We affirm the district court's holdings in all respects, except that we reverse the court's ruling that claims 1 and 3 of the '195 patent are enabled. We also vacate that part of the district court's judgment relating to infringement of those claims.

BACKGROUND[1]

Erythropoietin (EPO) is a protein consisting of 165 amino acids which stimulates the production of red blood cells. It is therefore a useful therapeutic agent in the treatment of anemias or blood disorders characterized by low or defective bone marrow production of red blood cells.

The preparation of EPO products generally has been accomplished through the concentration and purification of urine from both healthy individuals and those exhibiting high EPO levels. A new technique for producing EPO is recombinant DNA technology in which EPO is produced from cell cultures into which genetically-engineered vectors containing the EPO gene have been introduced. The production of EPO by recombinant technology involves expressing an EPO gene through the same processes that occur in a natural cell.

[1] The district court, in a detailed opinion, fully sets out the scientific and historical background relating to the patents at issue. *See Amgen*, 13 USPQ2d at 1741-58. Familiarity with that opinion is presumed.

THE PATENTS

On June 30, 1987, the United States Patent and Trademark Office (PTO) issued to Dr. Rodney Hewick U.S. Patent 4,677,195, entitled "Method for the Purification of Erythropoietin and Erythropoietin Compositions" (the '195 patent). The patent claims both homogeneous EPO and compositions thereof and a method for purifying human EPO using reverse phase high performance liquid chromatography. The method claims are not before us. The relevant claims of the '195 patent are:

> 1. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers.
>
> * * *
>
> 3. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 1 in a pharmaceutically acceptable vehicle.
>
> 4. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least about 160,000 IU per absorbance unit at 280 nanometers.
>
> * * *
>
> 6. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 4 in a pharmaceutically acceptable vehicle.

Dr. Hewick assigned the patent to GI.

The other patent in this litigation is U.S. Patent 4,703,008, entitled "DNA Sequences Encoding Erythropoietin" (the '008 patent), issued on October 27, 1987, to Dr. Fu-Kuen Lin, an employee of Amgen. The claims of the '008 patent cover purified and isolated DNA sequences encoding erythropoietin and host cells transformed or transfected with a DNA sequence. The relevant claims are as follows:

> 2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.
>
> * * *
>
> 4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2 or 3 in a manner allowing the host cell to express erythropoietin.
>
> * * *
>
> 6. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 5.
>
> 7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.
>
> 8. A cDNA sequence according to claim 7.
>
> * * *
>
> 23. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 7, 8, or 11 in a manner allowing the host cell to express said polypeptide.

24. A transformed or transfected host cell according to claim 23 which host cell is capable of glycosylating said polypeptide.

25. A transformed or transfected mammalian host cell according to claim 24.

26. A transformed or transfected COS cell according to claim 25.

27. A transformed or transfected CHO cell according to claim 25.

* * *

29. A procaryotic host cell stably transformed or transfected with a DNA vector according to claim 28.

PROCEDURAL HISTORY

On October 27, 1987, the same day that the '008 patent was issued, Amgen filed suit against Chugai and GI. It alleged that GI infringed the '008 patent by the production of recombinant EPO (rEPO) and by use of transformed mammalian host cells containing vectors with DNA coding for the production of human EPO, and that Chugai, as a result of a collaborative relationship with GI, had induced and/or contributed to the direct infringement of the '008 patent by GI. Amgen further sought a declaration that GI's '195 patent is invalid under 35 U.S.C. §§ 102, 103, and 112, or, in the alternative, that Amgen does not infringe the claims of the '195 patent, and a declaration that GI and Chugai's future activities in the production and sale of rEPO will infringe the '008 patent.[2]

[2] Amgen subsequently filed a complaint with the United States International Trade Commission alleging that Chugai's importation of rEPO, manufactured in Japan using genetically engineered host cells, violated Section 337 of the Tariff Act of 1930 (19 U.S.C. § 1337, 1337a). The Commission entered an order terminating the investigation for lack of subject matter jurisdiction. This court vacated and remanded, holding that the Commission should have treated the complaint on the

GI and Chugai answered and counterclaimed, asserting several affirmative defenses, including invalidity under 35 U.S.C. §§ 101, 102, 103, and 112; non-infringement; failure to make deposits at a public depository of biological materials allegedly necessary for enabling the best mode of practicing the invention; and unenforceability of the patent because of Amgen's alleged inequitable conduct before the PTO. GI also counterclaimed, alleging that Amgen infringed the '195 patent, asserting unfair competition, and seeking a declaratory judgment that the '008 patent was invalid and not infringed.

GI and Chugai then filed a joint motion for a partial summary judgment that Amgen infringed the claims of the '195 patent. Chugai also filed its own motion for summary judgment. On February 24, 1988, the district court grant GI's and Chugai's motion for partial summary judgment and, on January 31, 1989, the court granted Chugai's motion for partial summary judgment only to the extent of ruling that the '008 patent does not contain a process claim, an issue that is not now before us.

In response to Amgen's motion for a preliminary injunction, the district court, on February 7, 1989, issued an order finding that "Amgen had shown a reasonable likelihood of success on the merits of the validity of its patent; that it would suffer irreparable injury due to the needs of an incipient market and the attendant burdens on a new company; . . ." and that, as to the public interest, "recombinant EPO is an extraordinarily valuable medicine that promises marked relief from renal failure." Because of this public interest finding, the court determined that it would not enter an order to delay or prevent production or shipping of EPO, but would require the defendant GI to place with the court all profits from the sale of EPO.

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merits and not on jurisdictional grounds, and that the claims of Amgen's patent did not cover a process for producing rEPO. *Amgen, Inc.* v. *United States Int'l Trade Comm'n*, 902 F.2d 1532, 14 USPQ2d 1734 (Fed. Cir. 1990).

In order to expedite trial, the parties consented to trial before a magistrate. The judge entered judgment upon findings of fact and conclusions of law set forth by the magistrate. With respect to Amgen's '008 patent, the court held that claims 2, 4, and 6 are valid, enforceable and have been infringed by GI; that infringement was not willful; that claims 7, 8, 23-27, and 29 are invalid for lack of enablement under 35 U.S.C. § 112 but, if valid, were infringed by GI; that the '008 patent does not contain a process claim; and that Chugai has not infringed, contributorily infringed, or induced infringement of any claim of the '008 patent. The court also dismissed Amgen's complaint against Chugai.

With respect to GI's '195 patent, the court concluded that claims 1 and 3 are valid, enforceable, and have been infringed by Amgen; that Amgen has not infringed claims 2 and 5; that Amgen's infringement was not willful; and that claims 4 and 6 are invalid for indefiniteness under 35 U.S.C. § 112, but, if valid, were infringed by Amgen. The court also concluded that Amgen did not misues the '008 patent and that this was not an "exceptional" case under 35 U.S.C. § 285.

DISCUSSION

I. AMGEN's '008 PATENT (Lin)

A. *Alleged prior invention under 35 U.S.C. § 102(g)*

The first issue we review is whether the district court erred in finding that the claims directed to a purified and isolated DNA sequence encoding human EPO were not invalidated by the work of GI's Dr. Fritsch. Section 102(g) provides in relevant part that:

A person is entitled to a patent unless—

(g) before the applicant's invention thereof the invention was made . . . by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Defendants assert error in the district court's legal conclusion that in this case Lin's conception occurred simultaneously with reduction to practice. *See e.g., Hybritech Inc.* v. *Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376, 231 USPQ 81, 87 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). They claim that Fritsch was first to conceive a probing strategy of using two sets of fully-degenerate cDNA probes of two different regions of the EPO gene to screen a gDNA library, which was the strategy which the district court found eventually resulted in the successful indentification and isolation of the EPO gene. Defendants further claim that Fritsch conceived this strategy in 1981, was diligent until he reduced the invention to practice in May of 1984, and thus should be held to be a 102(g) prior inventor over Lin, who reduced the invention to practice in September of 1983.

Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Hybritech*, 802 F.2d at 1376, 231 USPQ at 87 (citing 1 *Robinson on Patents* 532 (1890)); *Coleman* v. *Dines*, 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir. 1985) (citing *Gunter* v. *Stream*, 573 F.2d 77, 80, 197 USPQ 482, 484 (CCPA 1978)).

Conception requires both the idea of the invention's structure and possession of an operative method of making it. *Oka* v. *Youssefyeh*, 849 F.2d 581, 583, 7 USPQ2d 1169, 1171 (Fed. Cir. 1988).

In some instances, an inventor is unable to establish a conception until he has reduced the invention to practice through a successful experiment. This situation results in a simultaneous conception and reduction to practice. *See* 3 D. Chisum, *Patents* § 10.04[5] (1990). We agree with the district court that that is what occurred in this case.

The invention recited in claim 2 is a "purified and isolated DNA sequence" encoding human EPO. The structure of this DNA sequence was unknown until 1983, when the gene was cloned by Lin; Fritsch was unaware of it until 1984. As Dr. Sadler, an expert for GI, testified in his deposition: "You have to clone it first to get the sequence." In order to design a set of degenerate probes, one of which will hybridize with a particular gene, the amino acid sequence, or a portion thereof, of the protein of interest must be known. Prior to 1983, the amino acid sequence for EPO was uncertain, and in some positions the sequence envisioned was incorrect. Thus, until Fritsch had a complete mental conception of a purified and isolated DNA sequence encoding EPO and a method for its preparation, in which the precise identity of the sequence is envisioned, or in terms of other characteristics sufficient to distinguish it from other genes, all he had was an objective to make an invention which he could not then adequately describe or define.

A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. *See Oka*, 849 F.2d at 583, 7 USPQ at 1171. Conception does not occur unless one has a mental picture of the

structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.

Fritsch had a goal of obtaining the isolated EPO gene, whatever its identity, and even had an idea of a possible method of obtaining it, but he did not conceive a purified and isolated DNA sequence encoding EPO and a viable method for obtaining it until after Lin. It is important to recognize that neither Hewick nor Lin invented EPO or the EPO gene. The subject matter of claim 2 was the novel *purified and isolated* sequence which codes for EPO, and neither Hewick nor Lin knew the structure or physical characteristics of it and had a viable method of obtaining that subject matter until it was actually obtained and characterized.

Defendants further argue that because the trial court found that the probing and screening method employed by Lin is what distinguished the invention of the '008 patent over the prior art, Fritsch's strategy in 1981 had priority over Lin's use of that strategy. We disagree. The trial court found that Fritsch's alleged conception in 1981 of an approach that might result in cloning the gene was mere speculation. Conception of a generalized approach for screening a DNA library that might be used to identify and clone the EPO gene of then unknown constitution is not conception of a "purified and isolated DNA sequence" encoding human EPO. It is not "a

definite and permanent idea of the complete and operative invention." Fritsch's conception of a process had to be sufficiently specific that one skilled in the relevant art would succeed in cloning the EPO gene. *See Coleman*, 754 F.2d at 359, 224 USPQ at 862. Clearly, he did not have that conception because he did not know the structure of EPO or the EPO gene.

The record indicates that several companies, as well as Amgen and GI, were unsuccessful using Fritsch's approach. As the trial court correctly summarized:

> Given the utter lack of experience in probing genomic libraries with fully degenerate probes and the crudeness of the techniques available in 1981, it would have been mere speculation or at most a probable deduction from facts then known by Dr. Fritsch that his generalized approach would result in cloning the EPO gene.

13 USPQ2d at 1760. As expert testimony from both sides indicated, success in cloning the EPO gene was not assured until the gene was in fact isolated and its sequence known. Based on the uncertainties of the method and lack of information concerning the amino acid sequence of the EPO protein, the trial court was correct in concluding that neither party had an adequate conception of the DNA sequence until reduction to practice had been achieved; Lin was first to accomplish that goal.

Defendants also argue that the court failed to consider that 1983, just prior to Lin's conception, was the relevant time for determining the completeness of Fritsch's conception, not 1981. However, the record shows that the court did consider what occurred in 1983. Moreover, Fritsch had no more of a conception in 1983 than he did in 1981, because he did not then know the sequence of the gene encoding EPO.

B. *Alleged Obviousness of the inventions of claims 2, 4, and 6*

Claim 2, as noted above, recites a purified and isolated DNA sequence, and claims 4 and 6 are directed to host cells transformed with such a DNA sequence. The district court determined that claims 2, 4, and 6 are not invalid under 35 U.S.C. § 103, concluding that the unique probing and screening method employed by Lin in isolating the EPO gene and the extensive effort required to employ that method made the invention nonobvious over the prior art.[3]

Obviousness under Section 103 is a question of law. *Panduit Corp.* v. *Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). The district court stated that one must inquire whether the prior art would have suggested to one of ordinary skill in the art that Lin's probing and screening method should be carried out and would have a reasonable expectation of success, viewed in light of the prior art. *See In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). "Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." *Id.*

The district court specifically found that, as of 1983, none of the prior art references "suggest[s] that the probing strategy of using two fully-redundant [sic] sets of probes, of relatively high degeneracy [sic], to screen a human genomic library would be likely to succeed in pulling out the gene of interest."[4]

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[3] We note that both the district court and the parties have focused on the obviousness of a process for making the EPO gene, despite the fact that it is products (genes and host cells) that are claimed in the patent, not processes. We have directed our attention accordingly, and do not consider independently whether the products would have been obvious aside from the alleged obviousness of a method of making them.

[4] At this point, some explanation of the involved technology may be useful, consistent with that expressed in the district court opinion. DNA consists of two complementary strands of nucleotides, which include the four basic compounds adenine(A), guanine(G), cytosine(C), and thymine(T), oriented so that bases from

13 USPQ2d at 1768. While it found that defendants had shown that these procedures were "obvious to try," the references did not show that there was a reasonable expectation of success. *See In re O'Farrell*, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988).

Defendants challenge the district court's determination, arguing that, as of September 1983, one of ordinary skill in the art would have had a reasonable expectation of success in screening a gDNA library by Lin's method in order to obtain EPO. We agree with the district court's conclusion, which was supported by convincing testimony. One witness, Dr. Davies of Biogen, another biotechnology company that had worked on EPO, stated that he could not say whether Biogen scientists would have succeeded in isolating the EPO gene if

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one strand weakly bond to the bases of the opposite strand. A bonds with T, and G bonds with C to form complementary base pairs. This bonding process is called hybridization and results in the formation of a stable duplex molecule. The structure also includes 5-carbon sugar moieties with phosphate groups.

The genetic code for a particular protein depends upon sequential groupings of three nucleotides, called codons. Each codon codes for a particular amino acid. Since there are four nucleotide bases and three bases per codon, there are 64 ($4 \times 4 \times 4$) possible codons. Because there are only 20 natural amino acids, most amino acids are specified by more than one codon. This is referred to as a "redundancy" or "degeneracy" in the genetic code, a fact that complicates and renders more difficult the techniques of recombinant DNA.

In order to prepare a protein using recombinant DNA technology, the gene for the protein must first be isolated from a cell's total DNA by screening a library of that cell's DNA. The DNA library is screened by use of a probe, a synthetic radiolabelled nucleic acid sequence which can be used to detect and isolate complementary base sequences by hybridization. To design a probe when the gene has not yet been isolated, a scientist must know the amino acid sequence, or portion thereof, of the protein of interest. Because some amino acids have several possible codons and the researcher cannot know which of the possible codons will actually code for an amino acid, he or she may decide to design a set of probes that covers all possible codons for each amino acid comprising the protein, known as a "fully-degenerate" set of probes. A library to be screened can be a genomic library (gDNA), which contains a set of all the DNA sequences found in an organism's cells or a complementary DNA (cDNA) library, which is much smaller and less complex than a gDNA library, and is used frequently when the tissue source for a given gene is known.

Biogen had the EPO fragments that were available to Lin in 1983. Dr. Wall, a professor at UCLA, testified that it would have been "difficult" to find the gene in 1983, and that there would have been no more than a fifty percent chance of success. He said, "you couldn't be certain where in the genomic DNA your probe might fall." The court found that no one had successfully screened a genomic library using fully-degenerate probes of such high redundancy as the probes used by Lin. In the face of this and other evidence on both sides of the issue, it concluded that defendants had not shown by clear and convincing evidence that the procedures used by Lin would have been obvious in September 1983. We are not persuaded that the court erred in its decision.

Defendants assert that whether or not it would have been obvious to isolate the human EPO gene from a gDNA library with full-degenerate probes is immaterial because it was obvious to use the already known monkey EPO gene as a probe. Defendants point out that, in the early 1980's, Biogen did significant work with an EPO cDNA obtained from a baboon, and that they used it as a probe to hybridize with the corresponding gene in a human gDNA library. However, this technique did not succeed until after Lin isolated the EPO gene with his fully-degenerate set of probes.

To support its obviousness assertion, defendants rely upon the testimony of their expert, Dr. Flavell, who testified that the overall homology of baboon DNA and human DNA was "roughly 90 percent." While this testimony indicates that it might have been feasible, perhaps obvious to try, to successfully probe a human gDNA library with a monkey cDNA probe, it does not indicate that the gene could have been identified and isolated with a reasonable likelihood of success. Neither the DNA nucleotide sequence of the human EPO gene nor its exact degree of homology with the monkey EPO gene was known at the time.

Indeed, the district court found that Lin was unsuccessful at probing a human gDNA library with monkey cDNA until after he had isolated the EPO gene by using the fully-degenerate probes. Based on the evidence in the record, the district court found there was no reasonable expectation of success in obtaining the EPO gene by the method that Lin eventually used. While the idea of using the monkey gene to probe for a homologous human gene may have been obvious to try, the realization of that idea would not have been obvious. There were many pitfalls. Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious. The district court thoroughly examined the evidence and the testimony. We see no error in its result. Moreover, if the DNA sequence was not obvious, host cells containing such sequence, as claimed in claims 4 and 6, could not have been obvious. We conclude that the district court did not err in holding that the claims of the patent are not invalid under Section 103.

C. Best Mode

Defendants argue that the district court erred in failing to hold the '008 patent invalid under 35 U.S.C. § 112, asserting that Lin failed to disclose the best mammalian host cells known to him as of November 30, 1984, the date he filed his fourth patent application.

The district court found that the "best mode" of practicing the claimed invention was by use of a specific genetically-heterogeneous strain of Chinese hamster ovary (CHO) cells, which produced EPO at a rate greater than that of other cells. It further found that this strain was disclosed in Example 10 and that Lin knew of no better mode. GI argues that Lin's best mode was not adequately disclosed in Example 10 because one skilled in the art could not duplicate Lin's best mode

without his having first deposited a sample of the specific cells in a public depository. The issue before us therefore is whether the district court erred in concluding that Example 10 of the '008 patent satisfied the best mode requirement as to the invention of the challenged claims[5] and that a deposit of the preferred CHO cells was not necessary.

A determination whether the best mode requirement is satisfied is a question of fact, *DeGeorge* v. *Bernier*, 768 F.2d 1318, 1324, 226 USPQ 758, 763 (Fed. Cir. 1985); we therefore review the district court's finding under a clearly erroneous standard.

35 U.S.C. § 112 provides in relevant part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, *and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

(Emphasis added).

This court has recently discussed the best mode requirement, pointing out that its analysis has two components. *Chemcast Corp.* v. *Arco Indus. Corp.*, 913 F.2d 923, 927, 16 USPQ2d 1033, 1036 (Fed. Cir. 1990). The first is a subjective one,

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[5] Defendants assert that all the claims should be invalid for failure to disclose the best mode. We perceive that the best mode issue only relates to the host cell claims, 4, 6, 23-27, and 29. Absent inequitable conduct, a best mode defense only affects those claims covering subject matter the practice of which has not been disclosed in compliance with the best mode requirement. *See Northern Telecom, Inc.* v. *Datapoint Corp.*, 908 F.2d 931, 940, 15 USPQ2d 1321, 1328 (Fed. Cir.), *cert. denied*, ___ U.S. ___, 111 S. Ct. 296 (1990).

asking whether, at the time the inventor filed his patent application, he contemplated a best mode of practicing his invention. If he did, the second inquiry is whether his disclosure is adequate to enable one skilled in the art to practice the best mode or, in other words, whether the best mode has been concealed from the public. The best mode requirement thus is intended to ensure that a patent applicant plays "fair and square" with the patent system. It is a requirement that the *quid pro quo* of the patent grant be satisfied. One must not receive the right to exclude others unless at the time of filing he has provided an adequate disclosure of the best mode known to him of carrying out his invention. Our case law has interpreted the best mode requirement to mean that there must be no concealment of a mode known by the inventor to be better than that which is disclosed. *Hybritech Inc.* v. *Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1384-85, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). Section 282 imposes on those attempting to prove invalidity the burden of proof. We agree that the district court did not err in finding that defendants have not met their burden of proving a best mode violation.

As noted above, the district court found that the best mode of making the CHO cells was set forth in Example 10. As the district court stated, while it was not clear which of two possible strains Lin considered to be the best, the cell strain subjected to 1000 nanomolar MTX (methotrexate) or that subjected to 100 nanomolar MTX, the best mode was disclosed because both were disclosed.[6] Defendants argue that this disclosure is not enough, that a deposit of the cells was required.

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[6] In its opinion, the district court stated that "the best way to express EPO was from mammalian cells . . . and that a cell line derived from 11 possible clones from the CHO B11 3,.1 cell strain was to be used for Amgen's master working cell bank, which was expected to be started on November 26, 1984." 13 USPQ2d at 1772. At another point, the court stated that Amgen "did disclose the best mode in Example 10 of the invention, when it described the production rates of the 100

Defendants contend that "[i]n the field of living materia. such as microorganisms and cell cultures," we should require a biological deposit so that the public has access to exactly the best mode contemplated by the inventor. This presents us with a question of first impression concerning the best mode requirement for patents involving novel genetically-engineered biological subject matter.

For many years, it has been customary for patent applicants to place microorganism samples in a public depository when such a sample is necessary to carry out a claimed invention. This practice arose out of the development of antibiotics, when microorganisms obtained from soil samples uniquely synthesized antibiotics which could not be readily prepared chemically or otherwise. *In re Argoudelis*, 434 F.2d 1390, 168 USPQ 99 (CCPA 1970). Such a deposit has been considered adequate to satisfy the *enablement* requirement of 35 U.S.C. § 112, when a written description alone would not place the invention in the hands of the public and physical possession of a unique biological material is required. *See, e.g., In re Wands*, 858 F.2d 731, 735-36, 8 USPQ2d 1400, 1403 (Fed. Cir. 1988) ("Where an invention depends on the use of living materials . . . it may be impossible to enable the public to make the invention (*i.e.*, to obtain these living materials) solely be means of written disclosure."); *In re Lundak*, 773 F.2d 1216, 1220, 227 USPQ 90, 93 (Fed. Cir. 1985) ("When an invention relates to a new biological material, the material may not be reproducible even when detailed procedures and a complete taxonomic description are included in the specification."); *see generally* Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement*, 67 J. Pat. & Trademark Off. Soc'y 569, 607 (1985) ("The deposit require-

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nanomolar-amplified cells (the B11 3,.1 cell strain) and one micromolar-treated cells." *Id.*

ment is a nonstatutory mechanism for ensuring compliance with the 'enabling' provison under 35 U.S.C. § 112.").

The district court found that the claims at issue require the use of biological materials that were capable of being prepared in the laboratory from readily available bioligical cells, using the description in Example 10. The court also found that there were no starting materials that were not publicly available, that were not described, or that required undue experimentation for their preparation in order to carry out the best mode. The court noted that Lin testified that the isolation of the preferred strain was a "routine limited dilution cloning procedure[ ]" well known in the art. Dr. Simonsen, GI's own expert, testified that the disclosed procedures were "standard" and that:

> with the vectors and the sequences shown in Example 10, I have no doubt that someone eventually could reproduce — well, could generate cell lines [sic, strains] making some level of EPO, and they could be better, they could be worse in terms of EPO production.

The district court relied on this testimony, and, upon review, we agree with its determination. The testimony accurately reflects that the invention, as it relates to the *best mode* host cells, could be practice by one skilled in the art following Example 10. Thus, the best mode was disclosed and it was adequately enabled.

These materials are therefore not analogous to the biological cells obtained from unique soil samples. When a biological sample required for the practice of an invention is obtained from nature, the invention may be incapable of being practiced without access to that organism. Hence the deposit is required in that case. On the other hand, when, as is the case here, the

organism is created by insertion of genetic material into a cell obtained from generally available sources, then all that is required is a description of the best mode and an adequate description of the means of carrying out the invention, not deposit of the cells. If the cells can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required. *See Feldman* v. *Aunstrup*, 517 F.2d 1351, 1354, 186 USPQ 108, 111 (CCPA 1975), ("No problem exists when the microorganisms used are known and readily available to the public."), *cert. denied*, 424 U.S. 912 (1976). Since the court found that that is the case here, we therefore hold that there is no failure to comply with the best mode requirement for lack of a deposit of the CHO cells, when the *best mode* of preparing the cells has been disclosed and the best mode cells have been enabled, *i.e.*, they can be prepared by one skilled in the art from known materials using the description in the specification.

Defendants also contend that the examiner's rejection of the application that matured into the '008 patent for failure to make a publicly accessible biological deposit supports its argument. U.S. Patent Application Serial No. 675,298, Prosecution History at 179 (First Rejection July 3, 1986). However, that rejection was withdrawn after an oral interview and a written argument that the invention did not require a deposit. *Id.* at 208.

We also note that the PTO has recently prescribed guidelines concerning the deposit of biological materials. *See* 37 C.F.R. § 1.802(b) (1990) (biological material need not be deposited "if it is known and readily available to the public or can be made or isolated without undue experimentation"). The PTO, in response to a question as to whether the deposit requirement is applicable to the best mode requirement, as distinct from enablement, said:

> The best mode requirement is a safeguard against the possible selfish desire on the part of some people to obtain patent protection without making a full disclosure. The requirement does not permit an inventor to disclose only what is known to be the second-best embodiment, retaining the best . . . . The fundamental issue that should be addressed is whether there was evidence to show that the quality of an applicant's best mode disclosure is so poor as to effectively result in concealment. *In re Sherwood*, 615 F.2d 809, 204 USPQ 537 (CCPA 1980). If a deposit is the only way to comply with the best mode requirement then the deposit must be made.

52 *Fed. Reg.* 34080, 34086 (Sept. 8, 1987).[7]

We see no inconsistency between the district court's decision, which we affirm here, and these guidelines.

Defendants also assert that the record shows that scientists were unable to duplicate Lin's genetically-heterogeneous best mode cell strain. However, we have long held that the issue is whether the disclosure is "adequate," not that an exact duplication is necessary. Indeed, the district court stated that

> [t]he testimony is clear that no scientist could ever duplicate exactly the best mode used by Amgen, but that those of ordinary skill in the art could produce mammalian host cell strains or lines with similar levels of production identified in Example 10.

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[7] *See also* 53 *Fed. Reg.* 39420, 39425 (Oct. 6, 1989) (comment *re* "deposit [to] satisfy the best mode requirement"); 52 *Fed. Reg.* 34080, 34080 and 34084 (Sept. 8, 1987) (deposit may be required to satisfy enablement, best mode, or distinct claim requirements of § 112).

13 USPQ2d at 1774. What is required is an adequate disclosure of the best mode, not a guarantee that every aspect of the specification be precisely and universally reproducible. *See In re Gay*, 309 F.2d 769, 773, 135 USPQ 311, 316 (CCPA 1962).

Defendants finally argue that Lin's failure to deposit the transfected cells notwithstanding the fact that he was willing to deposit essentially worthless cell material was evidence of deliberate concealment. We have already stated that deposit of the host cells containing the rEPO gene was not necessary to satisfy the best mode requirement of Section 112. The best mode was disclosed and a deposit was not necessary to carry it out. Therefore, the fact that some cells were deposited, but not others, is irrelevant.

D. *Enablement of claims 7, 8, 23-27, and 29*

Amgen argues that the district court's holding that GI "provided clear and convincing evidence that the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 of the '008 patent without undue experimentation" constituted legal error. 13 USPQ2d at 1776. Amgen specifically argues that the district court erred because it "did not properly address the factors which this court has held must be considered in determining lack of enablement based on assertion of undue experimentation," citing this court's decision in *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Claim 7 is a generic claim, covering all possible DNA sequences that will encode any polypeptide having an amino acid sequence "sufficiently duplicative" of EPO to possess the property of increasing production of red blood cells. As claims 8, 23-27, and 29, dependent on claim 7, are not separately argued, and are of similar scope, they stand or fall with claim 7. *See In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1900 (Fed. Cir. 1990) (in banc).

Whether a claimed invention is enabled under 35 U.S.C. § 112 is a question of law, which we review *de novo*. *Moleculon Research Corp.* v. *CBS, Inc.*, 793 F.2d 1261, 1268, 229 USPQ 805, 811 (Fed. Cir. 1986), *cert. denied*, 479 U.S. 1030 (1987). "To be enabling under § 112, a patent must contain a description that enables one skilled in the art to make and use the claimed invention." *Atlas Powder Co.* v. *E.I. duPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. *Id.* The essential question here is whether the scope of enablement of claim 7 is as broad as the scope of the claim. *See generally In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970); 2 D. Chisum, *Patents* § 7.03[7][b] (1990).

The specification of the '008 patent provides that:

> one may readily design and manufacture genes coding for microbial expression of polypeptides having primary conformations which differ from that herein specified for mature EPO in terms of the identity or location of one or more residues (e.g., substitutions, terminal and intermediate additions and deletions).
>
> * * *
>
> DNA sequences provided by the present invention are thus seen to comprehend all DNA sequences suitable for use in securing expression in a procaryotic or eucaryotic host cell of a polypeptide product having at least a part of the primary structural conformation and one or more of the biological properties of erythropoietin, and selected from among: (a)

> the DNA sequences set out in FIGS. 5 and 6; (b) DNA sequences which hybridize to the DNA sequences defined in (a) or fragments thereof; and (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) and (b).

The district court found that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substituting three amino acids. The patent indicates that it embraces means for preparation of "numerous" polypeptide analogs of EPO. Thus, the number of claimed DNA encoding sequences that can produce an EPO-like product is potentially enormous.

In a deposition, Dr. Elliott, who was head of Amgen's EPO analog program, testified that he did not know whether the fifty to eighty EPO analogs Amgen had made "had the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake." Based on this evidence, the trial court concluded that "defendants had provided clear and convincing evidence that the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 of the '008 patent without undue experimentation." 13 USPQ at 1776. In making this determination, the court relied in particular on the lack of predictability in the art, as demonstrated by the testimony of both Dr. Goldwasser, another scientist who worked on procedures for purifying urinary EPO (uEPO), and Dr. Elliott. After five years of experimentation, the court noted, "Amgen is still unable to specify which analogs have the biological properties set forth in claim 7." *Id.*

We believe the trial court arrived at the correct decision, although for the wrong reason. By focusing on the biological properties of the EPO analogs, it failed to consider the enablement of the DNA sequence analogs, which are the subject of claim 7. Moreover, it is not necessary that a patent applicant test all the embodiments of his invention, *In re Angstadt*, 537 F.2d 498, 502, 190 USPQ 214, 218 (CCPA 1976); what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims. For DNA sequences, that means disclosing how to make and use enough sequences to justify grant of the claims sought. Amgen has not done that here. In addition, it is not necessary that a court review all the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory. What is relevant depends on the facts, and the facts here are that Amgen has not enabled preparation of DNA sequences sufficient to support its all-encompassing claims.

It is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of Section 112. *See Utter* v. *Hirage*, 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. § 112 ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses."); *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) ("[R]epresentative samples are not required by the statute and are not an end in themselves."). Here, however, despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analog genes are disclosed. Amgen argues that this is sufficient to support its claims; we disagree. This "disclosure" might well justify a generic claim encompassing these and similar

analogs, but it represents inadequate support for Amgen's desire to claim all EPO gene analogs. There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them.

In affirming the district court's invalidation of claims 7, 8, 23-27, and 29 under Section 112, we do not intend to imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs.

The district court properly relied upon *Fisher*[8] in making its decision. In that case, an applicant was attempting to claim an adrenocorticotrophic hormone preparation containing a polypeptide having at least twenty-four amino acids of a specified sequence. Only a thirty-nine amino acid product was disclosed. The court found that applicant could not obtain claims that are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. § 112. It stated:

> Appellant's parent application, therefore, discloses no products, inherently or expressly, containing other than 39 amino acids, yet the claim includes all polypeptides, of the recited potency and purity, having at least 24 amino acids in the chain in the recited sequence. The parent specification does not enable

[8] *Cf. Hormone Research Foundation, Inc.* v. *Genentech, Inc.*, 904 F.2d 1558, 15 USPQ2d 1039 (Fed. Cir. 1990). In *Hormone Research*, this court, in a remand, directed the district court to consider the effect of *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 8 USPQ2d 1461 (Fed. Cir. 1989) and *In re Hogan*, 559 F.2d 595, 194 USPQ 527 (CCPA 1977) on *Fisher* in its enablement analysis. The facts of our case are distinguishable from those in *Hormone Research*, *United States Steel*, and *Hogan*.

> one skilled in the art to make or obtain ACTHs with other than 39 amino acids in the chain, and there has been no showing that one of ordinary skill would have known how to make or obtain such other ACTHs without undue experimentation. As for appellant's conclusion that the 25th to 39th acids in the chain are unnecessary, it is one thing to make such a statement when persons skilled in the art are able to make or obtain ACTH having other than 39 amino acids; it is quite another thing when they are not able to do so. In the latter situation, the statement is in no way "enabling" and hence lends no further support for the broad claim. We conclude that appellant's parent application is insufficient to support a claim as broad as claim 4.
>
> * * *
>
> [Section 112] requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons or ordinary skill in the art.

Fisher, 427 F.2d at 836, 839, 166 USPQ at 21-22, 24.

Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances,

we find no error in the court's conclusion that the generic DNA sequence claims are invalid under Section 112.

E. *Inequitable Conduct*

Defendants argue that the '008 patent claims are unenforceable as a result of an asserted misrepresentation of the number of probes Lin used for the monkey gene cloning described in Example 3 of his patent. Relying on the district court's finding that Lin had said that a "full set" mixture of 128 "EpV" probes[9] was used for money cDNA screening, whereas only a 16-member "subset" of the EpV mixture was actually used, defendants argue that the court ought to have found that the representations were material.

The essential elements of proof of inequitable conduct include intent to deceive and materiality. After finding threshold levels of materiality and intent, the trial court must balance the two and determine, in its discretion, whether inequitable conduct has occurred. *J.P. Stevens & Co.* v. *Lex Tex Ltd., Inc.*, 747 F.2d 1553, 1560, 223 USPQ 1089, 1092 (Fed. Cir. 1984), *cert. denied*, 474 U.S. 822 (1985). While we review an ultimate conclusion of inequitable conduct under an abuse of discretion standard, *Kingsdown Medical Consultants, Ltd.* v. *Hollister Inc.*, 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed. Cir. 1988) (in banc), *cert. denied*, 490 U.S. 1067 (1989), the underlying factual threshold findings are reviewed under a clearly erroneous standard.

Lin set out to clone the EPO gene by more than one method, including using degenerate human probes and monkey probes. It is not disputed that he did isolate the human EPO gene from a genomic library using two different 128-member pools of probes made from fragments of the human EPO protein. There-

[9] The probes designated "EpV" were from EPO amino acid sequence region 46-52.

after, he also attempted to use the human sequence probes to find the monkey EPO cDNA to be used later as a probe to hybridize with the human EPO gene. Example 3 of the '008 patent describes this work, indicating that the screening yielded seven positive clones. It also reports that a subset of the human EpV mixture was used for DNA sequencing work. When Lin published his monkey cDNA cloning work in a scientific journal, he also reported the use of 128 EpV probes to screen the monkey library. Lin screened the monkey library with the full mixture of 128 EpV probes and with one of eight subsets of probes which made up the full EpV mixture. In response to a question whether a subset of EpV probes was used in the first screening of the monkey cDNA library, Lin testified:

> I don't know which we used, the subset first or used the full set first. I cannot recall exactly. It looks like the subset was first defining the number, yes.

This answer constituted the sole basis for the court's finding that, "[a]t trial, Lin admitted he only used a subset of the EpV 128 probes in screening the cDNA library." 13 USPQ2d at 1778.

We consider that the district court's finding of an "admission" of misrepresentation in Lin's testimony and its conclusion that GI "presented clear and convincing evidence of a misrepresentation" was clearly erroneous. That Lin did not recall whether he first screened the monkey cDNA library with a full set of probes or a subset of probes, and his answer that "it looks like" he used the subset, are certainly not clear admissions that he only used a subset. However, the district court was correct in concluding that, even if there had been an erroneous statement, it was not material because Lin succeeded in cloning the EPO gene first with his use of the fully-degen-

erate probes. Thus, his testimony does not provide clear and convincing evidence that he misrepresented to the PTO the number of probes used. He did use 128-member probes as well as a subset. Moreover, this evidence does not create an inference of an intent to mislead. The court properly concluded that there was no inequitable conduct in prosecuting the '008 patent.

II. GI's '195 PATENT (Fritsch)

A. *Enablement of claims 1 and 3*

Amgen challenges the district court's determination that "the '195 patent enables a person of ordinary skill in the art to obtain homogenous EPO [including rEPO and uEPO] from natural sources" having a mean *in vivo* specific activity of at least 160,000.[10] 13 USPQ2d at 1794. Claims 1 and 3 contain the limitation that EPO have a specific activity of at least 160,000 IU/AU. The district court found, based upon expert testimony from both sides, that to those skilled in the art, in the absence of an express statement in the patent, the claims would be construed to refer to *in vivo* rather than *in vitro* specific activity. To support its challenge, Amgen asserts that the district court's determination is contradicted by GI's own bioassay data and by the district court's finding that "the '195 patent fails to enable the purification of rEPO." Amgen also asserts that the district court erred in relying solely on an *in vitro* measure of specific activity, having initially construed

[10] The potency of EPO in the '195 patent is stated as its specific activity, expressed as a ratio of International Units (which measures the ability of EPO to cause formation of red blood cells) per absorbance unit (the amount of light absorbed by a sample of EPO measured by a spectrophotometer at a given wavelength, 280 nonameters), *i.e.*, IU/AU.

the '195 claims as requiring an *in vivo* measure to avoid invalidity for indefiniteness.

35 U.S.C. § 112 requires that an invention be described "in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same." We review a determination of enablement as a question of law. *Moleculon Research Corp.* v. *CBS, Inc.*, 793 F.2d 1261, 1268, 229 USPQ 805, 811 (Fed. Cir. 1986), *cert. denied*, 479 U.S. 1030 (1987).

We do not consider the court's finding that the assay measurement was an *in vivo* one to be erroneous in view of the testimony it heard. That being the case, the question is whether the court erred in concluding that the claims requiring 160,000 IU/AU by an *in vivo* measurement were enabled. We conclude that it did err.

Defendants have produced no evidence that it ever prepared EPO with a specific activity of at least 160,000 IU/AU *in vivo* using the disclosed methods. In its report to the FDA, GI stated that it had purified uEPO material "to homogeneity" by subjecting partially purified uEPO material to reverse phase high performance liquid chromatography (RP-HPLC), the technique taught by Hewick in the '195 patent. The district court found that GI reported to the FDA that the specific activity of uEPO, based on *in vivo* bioassays, was only 109,000 IU/AU.[11] GI orginally arrived at the figure of 160,000 IU/AU by calculation, before it had the capacity of derive quantitative information from bioassays. Hewick subjected the EPO to RP-HPLC, and obtained an actual value of 83,000 IU/AU. After weighing the chromatograph, he found that "at least fifty percent" of the area under the chromatograph curve was attributable to something other than EPO. He then doubled the

[11] Defendants provided no evidence that faulty purification procedures or other missteps caused its failure to obtain 160,000 IU/AU *in vivo* material as claimed in the '195 patent.

83,000, and arrived at a theoretical specific activity of "at least about 160,000 IU/AU." That procedure, while possibly valid as a means for estimating the specific activity of a pure sample, does not establish that GI had a workable method for actually obtaining the pure material that it claimed.

Moreover, the work of others shows that Hewick did not enable the preparation of uEPO having an *in vivo* specific activity of at least 160,000, as the claims required. Dr. Kawakita, a scientist at Kummamoto University in Japan, reported an *in vivo* specific activity of 101,000 IU/AU when using RP-HPLC according to Hewick's method. This is similar to the 109,000 value reported to the FDA by GI. Kawakita did report a value of 188,000, but did not follow the teachings in the '195 patent. Defendants also rely on the testimony of Fritsch that "I've also seen further data in Chugai's PLA indicating additional urinary EPO preparation that had activities of 190,000, I believe, units per absorbance unit." However, the document to which Fritsch referred was not offered into evidence by GI after Amgen objected to its introduction and is not before us.

Defendants argue that Dr. Kung's uEPO test result of 173,640 IU/AU in an *in vitro* test supports the enablement of its claims. Amgen argues that an *in vivo* test result would only have been 65 percent of the *in vitro* result and thus would not have met the 160,000 IU/AU limitation of the claims. The district court relied on Kung, despite the demonstrated disparity between the results of *in vitro* and *in vivo* testing.

It is not absolutely clear to us that, for uEPO, the *in vivo* specific activity is 65 percent of the *in vitro* specific activity. Nonetheless, Kung's measurement, being *in vitro*, does not demonstrate enablement of the claimed invention, and that fact means that the court erred in finding enablement. Added to this fact is the difference that exists between the *in vivo* results

for rEPO and uEPO[12], and the other lack of support for the 160,000 limitation. Under these circumstances, we hold that the district court erred in accepting the *in vitro* data as support for claims containing what has been found to be an *in vivo* limitation.

In addition to the question of enablement regarding uEPO, the district court found that the only purification attempt on rEPO in the manner set out in the '195 patent failed to provide homogeneous EPO. The patent itself, in Example 2, discloses GI's purification efforts on rEPO and indicates that GI did not obtain purified rEPO. As the district court found, "[t]he patent does not contain any procedures . . . for purifying rEPO to the point that RP-HPLC will be successful." 13 USPQ2d at 1758. Thus, the patent fails to enable purification of either rEPO or uEPO.[13] *See In re Rainer*, 377 F.2d 1006, 1012, 153 USPQ 802, 807 (CCPA 1967) ("specification is evidence of its own inadequacy").

The burden of showing non-enablement is Amgen's, not GI's, but in the case of a challenged patent, when substantial discovery has occurred, and there is no credible evidence that the claimed purified material can be made by those skilled in the art by the disclosed process, and all evidence from both the inventor and his assignee and from third parties is to the contrary, we conclude that Amgen has met its burden to show that the claims have not been adequately enabled. We do not hold that one must always prove that a disclosed process operates effectively to produce a claimed product. But, under these circumstances, we conclude that the court erred in holding that claims 1 and 3 were properly enabled.

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[12] The court quoted Chugai to the effect that the *in vivo* activity of uEPO is 65 percent that of rEPO.

[13] Chugai's sample reported to the Food and Drug Administration was not purified by the disclosed process.

B. *Indefiniteness of claims 4 and 6*

The district court held claims 4 and 6 of the '195 patent invalid because their specific activity limitation of "at least about 160,000" was indefinite. Defendants challenge this holding, asserting that there is no evidence that claims 4 and 6 do not comply with the requirements of 35 U.S.C. § 112.

The statute requires that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed. *See Shatterproof Glass Corp.* v. *Libbey-Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985) (Claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits."). The district court found that "bioassays provide an imprecise form of measurement with a range of error" and that use of the term "about" 160,000 IU/AU, coupled with the range of error already inherent in the specific activity limitation, served neither to distinguish the invention over the close prior art (which described preparations of 120,000 IU/AU), nor to permit one to know what specific activity values below 160,000, if any, might constitute infringement. 13 USPQ2d at 1787. It found evidence of ambiguity in the fact that Chugai, GI's partner, itself questioned whether the specific activity value of 138,000 IU/AU for its own rEPO was within the claim coverage.

In prosecuting the '195 patent, GI disclosed to the examiner a publication by Miyake et al., which discloses a uEPO product having an *in vivo* specific activity of 128,620 IU/AU. When the examiner noticed this disclosure late in the prosecution, he rejected the '195 claims with a specific activity limitation of "at least 120,000" as anticipated by the Miyake et al. dis-

closure. It was only after the "at least 120,000" claims were cancelled that GI submitted the "at least about 160,000" claim language.

The court found the "addition of the word 'about' seems to constitute an effort to recapture . . . a mean activity somewhere between 120,000, which the patent examiner found was anticipated by the prior art, and [the] 160,000 IU/AU" claims which were previously allowed. Because "the term 'about' 160,000 gives no hint as to which mean value between the Miyake et al. value of 128,620 and the mean specific activity level of 160,000 constitutes infringement," the court held the "at least about" claims to be invalid for indefiniteness. 13 USPQ2d at 1787-88. This holding was further supported by the fact that nothing in the specification, prosecution history, or prior art provides any indication as to what range of specific activity is covered by the term "about," and by the fact that no expert testified as to a definite meaning for the term in the context of the prior art. In his testimony, Fritsch tried to define "about" 160,000, but he could only say that while "somewhere between 155[,000] might fit within that number," he had not "given a lot of direct considerations to that. . . ."

When the meaning of claims is in doubt, especially when, as is the case here, there is close prior art, they are properly declared invalid. *Standard Oil Co.* v. *American Cyanamid Co.*, 774 F.2d 448, 453, 227 USPQ 293, 297 (Fed. Cir. 1985). We therefore affirm the district court's determination on this issue. We also note that, in view of our reversal of the district court's holding that claims 1 and 3 are valid, it is clear that claims 4 and 6 would also be invalid without the "about" limitation. In arriving at this conclusion, we caution that our holding that the term "about" renders indefinite claims 4 and 6 should not be understood as ruling out any and all uses of this term in patent claims. It may be acceptable in appropriate fact situations, *e.g.*, *W.L. Gore & Assocs., Inc.* v. *Garlock,*

Inc., 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983) ("use of 'stretching . . . at a rate exceeding about 10% per second' in the claims is not indefinite"), even though it is not here.

C. *Inequitable Conduct*

The district court concluded that GI did not engage in inequitable conduct with respect to the '195 patent. Amgen challenges this holding, asserting, *inter alia*, that GI displayed an intent to mislead by withholding data showing *in vivo* specific activity of homogenous uEPO and withholding information on the range of error in EPO bioassays.

It is fundamental that to establish inequitable conduct, an intent to deceive is required. *RCA Corp.* v. *Data General Corp.*, 887 F.2d 1056, 1065, 12 USPQ2d 1449, 1456-57 (Fed. Cir. 1989). A finding of an intent to deceive may follow from an assessment of materiality, knowledge, and surrounding circumstances, including evidence of good faith. *Kingsdown Medical Consultants Ltd.* v. *Hollister Inc.*, 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1067 (1989). The district court found no such intent, stating:

> the record is devoid of any evidence that would establish deliberate knowing withholdings of any kind by Dr. Hewick or GI. Dr. Hewick was a credible witness who spoke carefully and candidly about his work . . . . There is no evidence that Dr. Hewick withheld any information he believed was material to the patent examiner.

Amgen, 13 USPQ2d at 1791. There is no clear error in this finding. Amgen raises no inequitable conduct issues that were

not fully considered by the district court. We have reviewed the record and find no abuse of discretion on the part of the district court. This is also not an exceptional case.

III. OTHER ISSUES

In view of our conclusion that the district court erred as a matter of law in holding that claims 1 and 3 of the '195 patent are not invalid, we vacate the district court's holdings relating to infringement of those claims. We have considered the other arguments by counsel on both sides and find them to be without merit.

CONCLUSION

We conclude that the district court did not err in its findings that claims 2, 4, and 6 of the '008 patent are valid and enforceable and have been infringed by GI, and that claims 7, 8, 23-27, and 29 of the '008 patent are invalid; we therefore affirm the judgment of the court regarding the '008 patent. Because we conclude that claims 1, 3, 4, and 6 of the '195 patent are invalid, we affirm the judgment concerning claims 4 and 6 and reverse the judgment concerning claims 1 and 3.

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART, REVERSED-IN-PART, VACATED-IN-PART

APPENDIX B

UNITED STATES DISTRICT COURT

DISTRICT OF MASSACHUSETTS

AMGEN, INC.
Plaintiff,

v. Civ. Action No. 87-2617-Y

CHUGAI PHARMACEUTICAL CO., LTD.,
AND GENETICS INSTITUTE, INC.,
Defendants.

MEMORANDUM AND ORDER

DECEMBER 11, 1989
(As corrected January 30, 1990)

SARIS, U.S.M.

I. INTRODUCTION

This action is about the highly competitive race between two leading biotechnology companies, among others, to clone the gene for the human hormone erythropoietin ("EPO"). A glycoprotein which stimulates red blood cell production, EPO is useful in the treatment of anemia, especially chronic anemia associated with end stage renal disease.

Plaintiff Amgen, Inc. ("Amgen"), a biotechnology company located in Thousand Oaks, California, was the first to clone the gene in October, 1983, when inventor Dr. Fu-Kuen Lin obtained the amino acid sequence for EPO and designed two sets of probes to isolate the EPO gene from a "genomic library," a mixture containing most, if not all, of the human genes.

Amgen filed an application for a patent on December 13, 1983 in the United States Patent and Trademark Office ("PTO"). After rejections by the various patent examiners of the claims in three prior applications, U.S. Patent No. 4,703,008 (the "'008 patent"), entitled "DNA Sequences Encoding Erythropoietin," was issued on October 27, 1987. The patent claims genetic materials and genetically engineered host cells useful in the recombinant production of erythropoietin.

Defendant Genetics Institute, Inc. ("GI"), a biotechnology company located in Cambridge, Massachusetts, was the second to clone the gene. Dr. Edward Fritsch, using a similar technique to Dr. Lin's, isolated the gene in July, 1984, and on January 3, 1985, GI filed its '258 patent application with the PTO. GI does not contest that Dr. Lin was the first actually to clone the gene, but, among other things, argues that Dr. Fritsch invented the methodology necessary to clone the gene in December, 1981 before Dr. Lin conceived of it and that by 1983 Dr. Lin's methodology was obvious. On May 9, 1989, the PTO declared an "interference" between the '258 application and the '008 patent.

GI is also the owner of U.S. Patent No. 4,677,195 (the "'195 patent"), entitled "Method for the Purification of Erythropoietin and Erythropoietin Compositions," which was issued on June 30, 1989, the patent application filed on January 11, 1985. Defendant Chugai Pharmaceutical Co., Ltd. ("Chugai"), a company located in Tokyo, Japan, is the exclusive licensee of this patent. Inventor Dr. Rodney M. Hewick claims as his invention, among other things, "homogeneous erythropoietin" which has certain weight and biological activity characteristics, and which rises as a single peak on reverse phase high performance liquid chromatography. On January 31, 1989, Judge William Young issued a Memorandum and Order granting partial summary judgment in favor of GI and Chugai on the claim that Amgen's EPO, manufactured through

recombinant methods, literally infringed the '195 patent. However, Judge Young did not rule on the validity of that patent. *See Amgen, Inc.* v. *Chugai Pharmaceutical Co., Ltd.*, 706 F. Supp. 94 (D. Mass. 1989) ("*Amgen*").

Among other things, Amgen argues that the '195 patent is invalid because the invention was obvious to those of ordinary skill in the art in 1984, and was anticipated by the prior art.

II. SUMMARY OF CONCLUSIONS OF LAW AND FACT

As the late Judge Charles Wyzanski so aptly wrote, patent cases are "so satisfactory to try" because "[t]he patent lawyer understands better than most of us that the mystery of the universe lies in the detail. And to make his lesson clearer the patent lawyer gives me the benefit of the instruction of the topnotch professors from the finest technological institutes." C. Wyzanski, Jr., "A Trial Judge," in *Whereas, A Judge's Premises* 5 (1965). After trying this case, where the quality of the lawyering has been so high and the expertise of the leading scientists in the fields of protein chemistry and recombinant DNA technology so remarkable, the court is in full agreement with Judge Wyzanski's assessment.

This case has posed many close and difficult legal and factual issues. After reviewing the parties' submissions and the evidence, and assessing the credibility of the witnesses, the court concludes as follows based on the facts in evidence:

'008 Patent

1. Defendants have *not* shown by clear and convincing evidence that the '008 patent is invalid as anticipated by Dr. Fritsch's EPO work at GI in 1981. (*See* p. [A94] *infra*).

2. Defendants have *not* shown by clear and convincing evidence that the '008 patent in invalid as obvious in 1983. (*See* p. [A108] *infra*).

3. Defendants have *not* shown by clear and convincing evidence that the '008 patent is invalid for failure to disclose the best mode of carrying out the invention, despite Amgen's failure to deposit a mammalian host cell with a publicly accessible depository. (*See* p. [A121] *infra*).

4. Defendants have demonstrated by clear and convincing evidence that claim 7 of the '008 patent and claims 8, 23-27 and 29, which are dependent on claim 7, are invalid under 35 U.S.C. § 112 because claim 7 does not enable one of ordinary skill in the art to practice the invention. (*See* p. [A133] *infra*).

5. Amgen did not engage in inequitable conduct before the patent office, and did not misuse the patent. (*See* pp. [A141, A144] *infra*).

6. Amgen has *not* shown that Chugai has infringed the '008 patent. (*See* p. [A146] *infra*).

7. GI has infringed the '008 patent. (*See* p. [A146] *infra*).

8. Amgen has *not* demonstrated willful infringement of the '008 patent. (*See* [A149] *infra*).

9. This is *not* an "exceptional case" which justifies the imposition of attorneys fees.

'195 Patent

1. Plaintiff has *not* shown by clear and convincing evidence that the '195 patent is invalid as anticipated under 35 U.S.C. § 102 (*See* p. [A150] *infra*).

2. Plaintiff has *not* shown by clear and convincing evidence that the '195 patent is invalid as obvious in light of the prior art. (*See* p. [A157] *infra*).

3. Plaintiff has *not* shown by clear and convincing evidence that claims 1 and 3 of the '195 patent should be invalidated

as indefinite. However, plaintiff has demonstrated that claim 4 of the patent and claim 6, which incorporates claim 4 by reference, are invalid as indefinite under 35 U.S.C. § 112. (*See* p. [A161] *infra*).

4. Amgen has *not* shown that defendants engaged in inequitable conduct in preparing or prosecuting the '195 patent application. (*See* p. [A170] *infra*).

5. Amgen has *not* shown by clear and convincing evidence that the '195 patent is invalid as non-enabling under 35 U.S.C. § 112. (*See* p. [A184] *infra*).

6. As decided by Judge Young on defendants' motion for partial summary judgment, defendants have established that Amgen has infringed claim 1, 3, 4 and 6 of the '195 patent. With respect to claims 2 and 5, judgment shall be entered on behalf of Amgen. (*See* p. [A190] *infra*).

7. Defendants have *not* shown that plaintiff has engaged in willful infringement of the '195 patent. (*See* p. [A190] *infra*).

8. This is not an "exceptional" case justifying an award of attorneys fees to defendants.

III. PROCEDURAL HISTORY

The instant action was filed on October 27, 1987 by Amgen against defendants Chugai and GI. Count I alleges that GI has infringed the '008 patent by the production of recombinant EPO ("rEPO") and by use of transformed mammalian host cells containing transforming vectors having recombinant DNA coding for the production of recombinant human EPO at its facilities in the District of Massachusetts; and that Chugai, as a result of a collaborative relationship with GI, has induced and/or contributed to the direct infringement of the '008 patent by GI. Count II seeks a declaration that the '195 patent is invalid under 35 U.S.C. §§ 102, 103, and 112. Count III seeks another declaratory judgment that defendants' future activities

under collaborative agreements related to rEPO will infringe the '008 patent.

On or about December 17, 1987, GI filed an answer which asserted sixteen affirmative defenses, including, invalidity of the '008 patent under 35 U.S.C. §§ 101, 102, 103, and 112; file wrapper estoppel; failure to make appropriate deposits at a scientific depository necessary to describe the best mode to practice the invention and to enable the invention; and the unenforceability of the patent because of Amgen's alleged inequitable conduct. GI also filed three counterclaims. The first counterclaim alleges infringement of the '195 patent. The second counterclaim asserts unfair competition. The third counterclaim seeks a declaratory judgment of the invalidity and noninfringement of the '008 patent.

On May 3, 1988, Chugai filed an amended answer and counterclaim. Chugai asserted the same affirmative defenses as GI and added a seventeenth affirmative defense that Amgen misused the '008 patent by attempting to extend the monopoly granted beyond any reasonable and justifiable interpretation of the claims by pursuing a complaint before the International Trade Commission ("ITC") in "bad faith." Chugai also asserted four counterclaims. Counterclaim one alleges infringement of the '195 patent by Amgen. Counterclaim two alleges unfair competition arising from Amgen's complaint in the ITC; Amgen's providing the Assistant Secretary of Commerce with "false and misleading information to the effect that Chugai had pirated Amgen's patented technology and was using such technology in Japan to compete unfairly with Amgen"; and Amgen's seeking an orphan drug designation pursuant to 21 U.S.C. § 360bb with the Food and Drug Administration ("FDA") without informing the FDA of the court's ruling in *Amgen* that Amgen had infringed the '195 patent. Counterclaim three seeks a declaratory judgment of invalidity and noninfringement of the '008 patent. Counterclaim four was brought

under section 2 of the Sherman Act, 15 U.S.C. § 2. Chugai contends that Amgen has illegally used the '008 patent in monopolizing and attempting to exclude Chugai from the rEPO market.

The day after Amgen brought this suit in Boston, GI and Chugai filed suit against Amgen, Ortho Pharmaceutical Corporation and Kirin-Amgen, Inc., a joint venture company of Amgen and the Japanese company, Kirin Brewery, in the Central District of California. Defendants counterclaimed for infringement of the '008 patent. This Los Angeles suit is the mirror image of the Boston suit insofar as the patent issues are concerned.

On February 24, 1988, after hearing oral argument, the trial court orally granted a motion for partial summary judgment brought by Chugai and GI on the claim that Amgen was infringing the claims of the '195 patent. Chugai filed a motion for summary judgement on May 12, 1988, seeking a determination that the '008 patent was unenforceable due to Amgen's alleged acts of patent misuse or, in the alternative, that the '008 patent contained no process claims, and thus did not cover Chugai's process of manufacturing recombinant erythropoietin. The court granted Chugai's motion for partial summary judgment only to the extent of ruling that the '008 patent does not contain a process claim. The written decision in *Amgen* was issued on January 31, 1989.

Meanwhile, the proceedings before the ITC were ongoing. Amgen filed its first complaint against Chugai with the ITC on January 4, 1988. After a period of discovery, on January 10, 1989, the administrative law judge made an "initial determination" that the "claims of the '008 patent do not cover a process which is used to manufacture EPO." On February 3, 1989, Amgen filed a second complaint with the ITC. On April 10, 1989, the ITC dismissed the first complaint for lack of subject matter jurisdiction. On May 23, 1989, the ITC decided not to institute an investigation based on Amgen's second complaint.

On January 24, 1989, the United States District Court for the District of Massachusetts issued a temporary restraining order enjoining defendants from, among other things, exporting, shipping or delivering to others certain recombinant EPO. On February 2, 1989, the court heard oral argument on plaintiff's motion for a preliminary injunction. At the outset, the trial judge noted that the case "cried out for a trial" by year's end. On February 7, 1989, the court issued an order finding that Amgen had shown a reasonable likelihood of success on the merits of the validity of its patent; that it would suffer irreparable injury due to the needs of an incipient market and attendant burdens on a new company; that the balance of equities was best struck by mandating an injunction that required the defendant GI to place with the court all profits of the sale of EPO; and that as to the public interest, "recombinant EPO is an extraordinarily valuable medicine that promises marked relief from renal failure." Because of this public interest, the court would not enter an order to delay or prevent production or shipping of erythropoietin.

In order to expedite a trial, the parties consented to trial before a magistrate. The case was referred to a magistrate on February 7, 1989. Discovery was expedited. The parties agreed to share documents and deposition transcripts produced during discovery before the ITC. Depositions took place as many as six days a week.

The bench trial commenced on August 7, 1989, and testimony concluded on October 19, 1989. Closing arguments were held on November 9, 1989. By agreement of the parties, the trial was bifurcated into a liability and damages phase. The court ordered that the parties' claims of "willfulness" would be litigated as part of the liability phase, and that all affirmative defenses would be considered in the initial stage, including charges of patent misuse. However, the court held that the counterclaims alleging unfair competition and antitrust violations would not be included in this phase.

IV. CLAIMS OF INFRINGEMENT

Amgen alleges that the following claims in the '008 patent have been infringed by defendants:

2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.

4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2 or 3 in a manner allowing the host cell to express erythropoietin.

6. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 5.

7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production or reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

8. A cDNA sequence according to claim 7.

23. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 7, 8 or 11 in a manner allowing the host cell to express said polypeptide.

24. A transformed or transfected host cell according to claim 23 which host cell is capable of glycosylating said polypeptide.

25. A transformed or transfected mammalian host cell according to claim 24.

27. A transformed or transfected CHO cell according to claim 25.

29. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 28.

Defendants allege Amgen has infringed the following claims in the '195 patent:

1. Homogenous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers.

3. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogenous erythropoietin of claim 1 in a pharmaceutically acceptable vehicle.

4. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least about 160,000 IU per absorbance unit at 280 nanometers.

6. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogenous erythropoietin of claim 4 in a pharmaceutic[a]lly acceptable vehicle.

V. GENERAL BACKGROUND CONCERNING PROTEINS[1]

a. The characteristics of EPO.

EPO is a hormone which is produced naturally in healthy individuals, and is the only hormone required for regulating the level of red blood cells which are found in the normal individual. (Tr. 1, 100). A hormone is a protein (also called a polypeptide) which is made in one cell, is secreted from that cell, and then acts on another cell in another organ. (*Id.*).

EPO is made in the kidney. (*Id.*). A small amount is also produced in the liver of adults and the liver of developing mammals — fetal liver. (*Id.*). It circulates from the kidney or liver through the blood stream to the sites where blood cells are made, usually the bone marrow and perhaps the spleen, to stimulate the production of red blood cells. (*Id.*). In the bone marrow, the EPO acts on standing populations of red blood cell precursors. (*Id.*). Precursors are cells which are committed to become red blood cells but which are not yet fully differentiated and released into circulation. (Tr. 1, 101).

EPO, as it exists in nature, is a very complex three-dimensional protein configuration consisting of 165 amino acids. (Tr. 1, 96-97). Altogether, there are twenty different amino acids, which, in their linear array, determine how proteins will fold and what their activity will be. (Tr. 1, 97-98). The amino acid sequence of EPO begins at residue 1, called the amino terminus or "n" terminus, and ends at residue 165, called the carboxyl terminus. (Tr. 1, 97). A residue is another term for an amino acid. (Tr. 1, 99).

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[1] The trial transcripts are cited with the first figure reflecting the volume, and the figures following the comma reflecting the pages. The notation "AF" stands for Amgen's proposed findings of fact. The notation "DF" stands for defendants' proposed findings of fact. Deposition transcripts ("Dep. Tr.") are separately cited with the name of the deponent given.

EPO is a glycoprotein. That means that sugar residues capped with a molecule called sialic acid are linked to a particular amino acid. (Tr. 1, 98-102). There are four glycosylation sites in the EPO protein. (PX 288). In addition, there are two disulfide bridges between amino acids, which are important covalent bonds necessary to ensure the proper folding of the molecule. (Tr. 1, 103). In the absence of glycosylation and the disulfide bridges, the EPO molecule is not very stable and is not very active in the body. (Tr. 1, 103). The protein EPO is depicted in Figure A.

b. <u>The cellular processes for synthesizing proteins.</u>

A cell is a very complicated structure. (Tr. 3, 14; DX 751). Within each cell is a nucleus that contains chromosomes. (*Id.*). DNA is the genetic material in the chromosomes which controls and determines all of the things that an organism does or is. (Tr. 1, 105-106). It encodes the proteins of the cell and it also contains the information for directing its own replication or growth. (Tr. 2, 4). It is found in every cell in the human body. (Tr. 2, 4).

DNA is a very long linear arrangement of nucleotides, which are also called bases. (Tr. 1, 106). There are only four nucleotides: adenine (A); guanine (G); cytosine (C) and thymine (T). (Tr. 2, 15). These bases are also present in RNA, except that thymine is substituted by a base called uracil (U). (Tr. 2, 15).

DNA is composed of two complementary strands which coil around each other in a double helix, called the Watson-Crick double helix. (Tr. 2, 32-33). If adenine is the base in one chain, the corresponding base in the other complementary chain will be thymine; and if cytosine is the base in one chain, the corresponding base in the complementary chain will be guanine. (Tr. 3, 16). These are called the complementary base pairs. (*Id.*).

A gene contains a unique DNA sequence of these A's, G's, C's and T's which code for a particular protein like EPO. (Tr. 1, 106-107). A gene is the segment of the double helix which has the information to enable the cell to make a particular protein. (Tr. 3, 19). Each double helix contains thousands of genes, each of which encodes a different protein. (Tr. 3, 20). The coding sequences in a gene are called exons. (Tr. 1, 108). There are regions in the gene between the exons, called introns, which do not code for the protein. (Tr. 1, 108). Introns are sometimes called intervening or silent sequences.

Surrounding the nucleus is the cytoplasm where proteins are made (Tr. 3, 17). The synthesis of proteins takes place over a series of several steps. The first step is the creation of messenger RNA ("mRNA") in the nucleus from strand of the double helix. For every A on the chain, the mRNA gets a complementary base of U; and for every G on the strand, the mRNA gets a C. The MRNA reflects the DNA sequences of the exons in a gene, not the introns. (Tr. 2, 45). Every three bases in the mRNA forms a codon, which specifies a particular amino acid in the protein. (Tr. 3, 21). The mRNA which is produced in the nucleus then travels to the cytoplasm where the gene is made. (Tr. 3, 22).

The cell's mechanisms, like the ribosome, which is an organelle in the cytoplasm, read the codons in the mRNA to determine what amino acids are necessary to synthesize the gene. (Tr. 3, 22-23). The cell manufactures a type of RNA called

transfer RNA ("tRNA") which has a complementary base pair to the mRNA. (Tr. 3, 24-25). There is a tRNA for each codon in the mRNA. (Tr. 3, 24). The tRNAs are the adapters which read the codon sequences by using a complementary codon to put the proper amino acids in place. (Tr. 3, 25). For example, if the condon is CGC, the cell knows that the next amino acid needed for the protein chain is the amino acid arginine. (Tr. 3, 22). Through the tRNAS, the amino acids are added to the chain one at a time, and when the gene is completely read, the protein or polypeptide has been made. (Tr. 3, 25). Three are special codons on the mRNA which are stop signals. (Tr. 3, 25-26).

The EPO gene, containing about 4,000 nucleotides, is not a very large gene by most standards. (Tr. 1, 107-108). This is one of the reasons it was a good candidate for cloning in 1981. (Tr. 3, 117). The DNA sequences in the EPO gene are set forth in Figure 6A-E of the '008 patent. (PX 2). Figure 4 of the '008 patent depicts the exons as black boxes on the "arcuate" or curvy line; the introns are the lines between those boxes. (*Id.*).

c. Recombinant technology for the production of protein.

A rough sketch of the technology used prior to 1983 for cloning a gene will provide useful background for understanding the claimed inventions here. Cloning a gene means obtaining or "isolating" the portion of the double helix which contains the DNA sequences that the cell uses to create a particular protein, and pulling it out or "purifying" it. (Tr. 3, 26, 33-34).

In order to isolate a gene, a microbiologist must screen a library (also called a pool or bank). (Tr. 3, 28-29). There are essentially two kinds of libraries. A genomic ("gDNA") library is a liquid solution which ideally contains a set of all the DNA sequences present in all the genes found in the nucleus of our bodys' cells, although there is never complete certainty that

every gene is represented. (Tr. 3, 28; 7, 80-81). DNA in chromosomes would be meters long if it were stretched out. (Tr. 3, 71). It is broken up into convenient pieces for the process of cloning using enzymes called "restriction enzymes." (Tr. 3, 71). In 1981 and 1982, there was general agreement in the scientific community that the genomic library prepared by Dr. Thomas Maniatis, one of the founders of GI, was a good library. (Tr. 3, 29-30). A scientist could predict that the gene of interest might be in the billions of sequences contained in that genomic library. (Tr. 3, 30).

Another kind of library is a complementary DNA ("cDNA") library, which is much smaller and less complex than the genomic library. cDNA is a DNA copy that has been made in a test tube with an enzyme that reproduces the information in mRNA. (Tr. 2, 31). It is made from the messenger RNA of a particular cell or tissue type. (Tr. 25, 67). To construct such a library, the tissue source for a given gene must be known. (Tr. 25, 67). By going to the mRNA in a tissue source for a given gene, a scientist has significantly reduced the overall complexity of the cloning project because only a small portion of the human genome will actually be expressed as messenger RNA. (Tr. 25, 67). A cDNA library is a much smaller haystack to screen than a gDNA library. (Tr. 25, 68). Moreover, because the cDNA is made from mRNA, there are no introns in the cDNA and a scientist is not faced with the problem of probes which do not hybridize properly because they "span" an intron. (Tr. 25, 73).

An oligonucleotide probe, which is a probe involving a short sequence of nucleotides, can be used to screen a library and to isolate a gene. Prior to 1983, there were three approaches to designing a probe. (Tr. 25, 81). To design a probe where the gene has not yet been isolated, a scientist must know the amino acid sequence of the protein of interest, or a portion of that sequence. In 1981, scientists had a table which told them

the codons that code for each amino acid. (Tr. 3, 39). Some amino acids have many different possible codons. For example, there are four different possible codons (sets of three bases) that can code for the amino acid valine which is contained in the protein EPO: CAA, CAT, CAG and CAC. (Tr. 3, 40). Before the gene encoding the EPO protein is cloned, a scientist cannot know which of the four codons will actually code for valine. (Tr. 3, 40). Therefore, in designing probes to screen a library for EPO, a scientist would have to decide whether to cover all the possible groups of three that can code for valine. (Tr. 3, 41). A "fully degenerate" set of probes is a set of probes which covers all of the possible groups of three nucleotides that code for each of the particular amino acids comprising the protein. (Tr. 3, 41). By the end of 1981, there were reports that oligonucleotide probes which were fully degenerate were being used to screen a cDNA library, but not a genomic library. (Tr. 25, 76-77).

Another strategy in designing probes is to design a "guess mer." (Tr. 25, 77). A mer is a nucleotide. (Tr. 25, 79). Scientists in 1981 and 1982 knew from "codon usage" principles that certain codons usually coded for a particular amino acid; therefore, rather than designing a fully degenerate set of probes which would anticipate every possible variation, a scientist would adopt the strategy of designing a probe that contained the most likely codons. (Tr. 5, 62, 102-104). These probes were usually long, between 30 and 88 nucleotides, because longer probes increase the change of hybridization even if there is a wrong guess in a few places. (Tr. 25, 80-81).

In choosing the amino acid sequence from which the probes will be designed, a microbiologist will choose the sequence with the least degeneracy, *i.e.*, with the smallest possible number of codon variations. If an amino acid sequence contains a large number of amino acids with highly degenerate codons, it is very difficult to design a completely degenerate probe. (Tr. 3, 60).

The most commonly used type of probe, and the most successful, at the end of 1981 was a single long probe, based on a cDNA clone that was already isolated or an already isolated portion of the genomic clone. (Tr. 25, 75). This gene would have a perfect homology with the gene of interest. (Tr. 25, 75). These kinds of probes were used to screen both cDNA and gDNA libraries. (Tr. 25, 76).

In order to screen a library, the DNA in the library must first be denatured to separate the double helix into two single strands so that a probe may bond or hybridize with a complementary strand. (Tr. 2, 120-121). Also, the library must be "plated." This means that a library containing a virus called a phage, which also contains the human DNA gene, is mixed with bacteria on agar on a plate. (Tr. 25, 87-89). The virus kills the bacteria, leaving holes; each hole contains viruses with the DNA. (Tr. 25, 88). A plate will have about 5,000 viruses and small holes. (Tr. 25, 89). The DNA is transferred onto filter paper, amplified, fixed to the filter paper, and subjected to prehybridization steps. (Tr. 25, 90-96). It is then ready for hybridization.

After the probe is synthesized, a radioactive atom is attached to the probe. (Tr. 25, 97). The solution containing the probe is poured into a prehybridization solution, and the probe diffuses through the liquid and finds the DNA bound to the filter paper. (Tr. 25, 98-99). If there is a good match, the probe will stick to the filter paper. (Tr. 25, 99). This matching is called hybridization, or the bonding of complementary sequences of two separate strands. (Tr. 25, 99). After two or three days of hybridization, the probes that have not hybridized are poured out into a waste container. (Tr. 25, 101). The filter papers are exposed to x-ray film. (Tr. 25, 102). When the probe hybridizes with the matching gene on the filter, an x-ray will reveal a dark spot produced by the radioactive atom. (Tr. 25, 97).

A high background of radioactivity can cause the x-ray film to darken to the point where it is difficult, if not impossible, to discern positive hybridizations. (Tr. 25, 105-106). Moreover, in isolating a gene with probes which are based on only part of the sequence encoding for the desired protein, it is possible that those probes also may bind with identical portions of a gene for other proteins, creating "false positives." (Tr. 25, 117-118).

At that point, the scientist can simply rescreen the filter with a second set of probes from another region of the gene if he has a second set. (Tr. 25, 108). Then the clones which hybridize with both sets of probes can be picked. (Tr. 25, 109). Alternatively, the "positive" clones can be plucked out and plated, and these can be screened with the second set of probes. (Tr. 25, 109). Various steps are undertaken to confirm that the positive clones contain the gene of interest. (Tr. 25, 110-114).

Once a probe or set of probes screens the genomic library and isolates the gene of interest, the gene is inserted or spliced into a plasmid or vector, which is simply a piece of DNA. (Tr. 3, 69; DX 754). This is another step in the process of cloning. (Tr. 3, 76).

The recombinant production of a protein like EPO begins with this cloned gene. The recombinant plasmid or vector with the inserted gene — the cloned gene — is then introduced, or "transfected", into a host cell. (Tr. 3, 69, 77). The host cell at that point is "transformed," also known as "transfected." (Tr. 2, 34). The vector or plasmid is the carrier which brings the DNA or gene of interest into the host cell, and allows the DNA to grow and replicate as the host cell grows and replicates. (Tr. 3, 73). This method for causing a host cell to express a protein is known as recombinant technology. (Tr. 3, 75).

In a laboratory setting, millions of host cells are exposed to a large number of identical plasmids or vectors with the in-

serted gene. (Tr. 3, 76-77). Some of the cloned genes will make it into some of those million cells. (Tr. 3, 77). They enter the cells through different points in the cell membrane, and lodge at different points within the cell, some in the cytoplasm and some in the nucleus. (Tr. 3, 78). Some cells receive no cloned genes and some receive more than one. (Tr. 3, 79-81). The result is a heterogeneous cell population with a wide variation in cellular characteristics, or "phenotype." (Tr. 3, 79). Among other things, the cells differ insofar as the DNA persists, and the amount of EPO, or other protein, produced. (Tr. 3, 80).

There are two kinds of host cells, prokaryotic and eukaryotic. Eukaryotic cells are mammalian, and prokaryotic cells are bacterial. (Tr. 3, 70). A prokaryotic cell does not have its DNA in the nucleus. One example of a prokaryotic cell is E. Coli. (Tr. 25, 114). One disadvantage to the E. Coli system is that it is not capable of adding the n-linked glycosylation onto a polypeptide chain. (Tr. 25, 115). This means the polypeptide, or protein, will not be biologically active *in vivo*. (Tr. 25, 115). There are different kinds of mammalian host cells. One kind is the chinese hamster ovary ("CHO") cell, which is the host cell used for the stable transformation and expression of EPO. (Tr. 2, 51). Another is the COS-1 cell which is a monkey cell. (Tr. 2, 48). The vector that is used to transfect the COS cell does not become stably transformed, but instead is maintained as a circular DNA molecule. (Tr. 2, 48). This particular state of the DNA is not stable and over a period of time the DNA in that COS cell, while expressing EPO or some other protein early on, will be lost from the cells. (Tr. 2, 48). It is called a transient transfection or a short-term expression system. (Tr. 2, 48).

In order to determine which cells among the heterogeneous cell population have been transfected, the methotrexate ("MTX") amplification process is used. (Tr. 3, 81). MTX is an

inhibitor of an enzyme called dihydrofolate reductase ("DHFR"). (Tr. 2, 51). DHFR is an enzyme, a protein, that plays a very important role in the production of the bases for DNA, for nucleus synthesis and for the growth of cells. (Tr. 2, 52; 6, 63). The DHFR gene is included in the vector which also contains the gene for the protein of interest, here EPO. (Tr. 3, 79-81). It is introduced into host cells which do not contain DHFR ("DHFR−"). By December, 1983, gene amplification utilizing MTX was commonly known and was a published procedure. (Tr. 2, 52).

The first step in the gene amplification process is that MTX kills all the cells which have not received the cloned gene, contained in the vector also carrying the DHFR. (Tr. 3, 81). Then the concentration of MTX is increased, thereby reducing the growth of cells because it prevents them from making nucleic acid. (Tr. 6, 62). The process of increasing the MTX concentration is called amplification. (Tr. 3, 84). As the MTX concentration is increased, the cells go into a state of crisis, which may last one through three weeks; those cells which amplify or increase their DHFR genes are able to make more of the enzyme DHFR and therefore are able to escape death by the inhibitor MTX. (Tr. 2, 54; 3, 83; 6, 63). Eventually, through this process, cells are arrived at in which the DHFR gene as well as any gene which is close to it in the vector will be amplified perhaps a hundred or a thousand times. (Tr. 2, 54). That large increase in gene number is related to a large increase in the amount of product that those genes can produce. (Tr. 2, 55). After MTX selection, the population of cells is still heterogeneous in that some transformed host cells may have a hundred copies of the gene while other cells may have a thousand or just ten. (Tr. 2, 55).

From the heterogeneous population of cells which have their genes amplified, "clones" — that is, individual, specialized cells making the protein — must be isolated. (Tr. 3, 84). A procedure called "limited dilution cloning," which was regu-

larly used in 1983, is employed to separate each cell into a "cell well." (Tr. 2, 53-56). Every cell that grows up as a daughter cell from that single cell is now a clone of the original parental cell. (Tr. 2, 55). The cell which produces the most protein is isolated. (Tr. 2, 55).

The purpose of gene amplification and limited dilution cloning is to obtain a clone, defined as a progeny of the cell which was transfected with the cloned gene, with a very high level of expression of recombinant protein, like erythropoietin. (Tr. 2, 54). These "amazon" clones are allowed to grow back up into a homogeneous population. (Tr. 2, 56).

Once human EPO is expressed in mammalian cells, an "assay", or experiment, must be performed to determine the "potency" or "activity" of the EPO. An "*in vitro*" assay is carried out in a test tube with the bone marrow cells from an animal. Bone marrow is the source of the precursor cells for the production of red blood cells, among other things. The EPO activates the red blood cell precursors, causing them to proliferate and differentiate. (Tr. 4, 79). One red blood cell turns into thousands of cells, and the *in vitro* culture turns red with hemoglobin. (Tr. 4, 79). The extent to which the cells incorporate radioactive iron, which is a component of the hemoglobin, is a measure of the activity of the EPO. (Tr. 4, 80).

Another kind of assay is the *in vivo* bioassay. (Tr. 4, 82). This type of assay involves the injection of EPO into an animal, like a mouse, to determine whether the animal will increase the production of red blood cells, and thereby increase the incorporation of the radioactive iron into the red blood cells. (Tr. 4, 82).

VI. CLONING AND EXPRESSION OF EPO

a. Cal Tech-1981

The quest for the EPO gene began at the California Institute of Technology ("Cal Tech") when Dr. Rodney Hewick sequenced

erythropoietin obtained from Dr. Eugene Goldwasser to 26 amino acid residues in the fall of 1980. (Tr. 10, 130-131; 11, 29-30). Hewick took the sequence with him to GI when he was employed to work there in 1981. (Tr. 10, 118; 11, 17-18; PX 588, p. 006750). In retrospect, the sequence obtained by Hewick contained question marks at positions 3 and 7. (Tr. 11, 19-20; PX 588, p. 006750). The sequence also contained an error at position 24, where Hewick had put the symbol "K" for lysine rather than the symbol for the correct amino acid residue, asparagine. (Tr. 11, 22-23; PX 588, p. 006750). The rest of the sequence was the actual EPO sequence from the n-terminus. (Tr. 11, 23).

The sequence derived by Dr. Hewick was presented at the 23rd annual meting of the American Society of Hematology in San Antonio, Texas, on December 6, 1981, by Dr. Goldwasser. (Tr. 11, 23-24; 27, 48; PX 531). Also, the sequence was published in June 1983 in an article by Drs. Sue and Sytkowski. (Tr. 11, 24; PX 531). In the Sue and Sytkowski published sequence, the third amino acid residue was properly assigned to proline. (*Id.*). However, there were errors at positions 7 and 24. (Tr. 11, 25).

b. Amgen.

Dr. Fu-Kuen Lin is the inventor of the '008 patent. (PX 2). Dr. Lin received a BS degree from the National Taiwan University in 1964, and a masters degree in 1967. (Tr. 4, 18). He received a PhD in 1971 from the University of Illinois in the physiology of fungi and then took a postdoctoral position at Purdue University from 1971 to 1973 in cancer research. (Tr. 4, 19). From 1973 to 1975, he was a postdoctoral associate at the University of Nebraska, also in cancer research; after returning to Taiwan for two years, he went to Louisiana State University from 1977 to 1979 where his research included nucleic acid sequencing of tRNA. (Tr. 4, 19-21) . From 1979 to 1981, he worked at the Medical University of South Carolina

where he cloned the duck globin gene from the genomic library of duck DNA using a probe made from the mRNA for the globin. (Tr. 4, 22). He joined Amgen on August 6, 1981, and was one of only seven scientists there. (Tr. 4, 23).

When Lin joined Amgen, he began to work on the EPO project which was already underway. (Tr. 4, 23). He was project leader of the EPO project from 1981 through 1984. (Tr. 4, 46; 6, 66). His assistant was Chi-Hwei Lin, no relation. (Tr. 4, 67). Other than the work done by others in doing protein and nucleic acid sequencing, Lin and his assistant were initially the only two working on the EPO project. (Tr. 5, 33). However, when Lin first arrived at Amgen, there was a woman scientist Maureen Gilmore-Hebert who had been working on the EPO project but who had decided to leave, and who did not work on the EPO project after Lin arrived there. (Tr. 5, 79-80). From 1981 to 1983, when the gene was finally cloned, Lin worked between ten and sixteen hours a day, and often six or seven days a week. (Tr. 4, 66).

In 1981, Amgen had some partial, ambiguous information about the n-terminal amino acid sequence of erythropoietin. (Tr. 4, 24). In his early days at Amgen, Lin outlined the research approach for the EPO project, and among other things, immediately started work on designing probes. (Tr. 4, 24).

Dr. Marty Cline, a professor from the University of California, Los Angeles, and a member of Amgen's Scientific Advisory Board, was involved with the EPO project. (Tr. 4, 25-26). During the September-October 1981 time frame, Lin discussed with Marty Cline this strategy for the EPO project, and in particular "the general approach" of using two sets of probes to screen genomic libraries. (Tr. 4, 26; 5, 65-67). Cline took notes about Lin's strategy. (Tr. 5, 18-19). At his deposition during the course of the ITC proceedings, Marty Cline identified certain handwritten notes dated and taken on October 27, 1981 as his handwriting. (PX 170, p. 46; PX 170A). These notes contain the following passage:

II. Phase 2: Jan-Mar 1982.

1. synthesize additional probes if possible and if necessary

2. screen cDNA libraries with 2 sets of probes

3. if screening of cDNA is negative begin screening of genomic libraries.

(PX 170A, 170B).

Lin remembers discussing with Cline prior to October 27, 1981 the screening of cDNA libraries with two sets of oligonucleotide probes. (Tr. 4, 32). He also remembers discussing the screening of genomic libraries with two sets of probes with Cline prior to October 27, 1981. (Tr. 4, 33). By two sets of probes, Lin testified he meant two sets of probes made from different regions of the EPO gene, and that the sets of probes could be fully or partially degenerate. (Tr. 4, 34). However, the notes do not state whether the probes would be fully degenerate, and Lin does not recall whether he used the words "fully degenerate" when talking to Cline. (Tr. 5, 64, 69). Although he was deposed and testified at the ITC proceedings, and was deposed as part of this action, Lin never mentioned this conversation with Dr. Cline until he testified at trial, and said he could not recall any conversations about his approach. (Tr. 5, 70-71). He reviewed the Cline notes prior to his trial testimony, and they refreshed his recollection. (Tr. 5, 72).

On April 28, 1982, Lin wrote a memorandum concerning an EPO project team meeting on April 23, 1982. (PX 170C). Lin wrote: "We urgently need a second region of amino acid sequence to confirm our clones." Later in the memorandum, after describing the alternative routes to looking for the EPO gene, Lin stated: "But it is agreed that confirming genomic clones with a probe from a second region of amino acid sequence is more direct and less time consuming." At the time, Amgen already had a number of putative EPO genomic clones,

and needed to find a way to identify which was the real EPO gene. Although there were several ways to confirm the gene, many were very time consuming. (Tr. 4, 38). Lin believed the more direct way to find the real EPO gene was to find an amino acid sequence from a different region of the EPO protein and to design a probe from that region which would give a second site of confirmation. (Tr. 4, 36-38).

Between October, 1981 and April, 1982, Lin only had n-terminal sequence information for EPO from amino acid 1 through amino acid 26. (Tr. 4, 43). Lin made many attempts to design probes from the amino acid information in this region of the gene, but none were successful in isolating the gene. (Tr. 4, 44-46; PX 63-19; PX 63-20). In retrospect, the reason the probes from the n-terminal sequence were unsuccessful in hybridizing with the EPO gene was that there were mistakes in the amino acid sequence information. (Tr. 4, 54).

Beginning in 1981 and continuing through 1982 and 1983, Lin worked with already existing clones to create a model system which could be used to probe for a gene that had not previously been cloned. (Tr. 5, 112-113). One of the conditions explored was the number of probes that could be used. (Tr. 5, 113).

Lin's initial strategy in September, 1981 and continuing through 1982 was to design probe sequences with the highest probability of success rather than to use fully degenerate sequences. (Tr. 6, 28-29, 48; DX 405).

On September 24, 1981, Lin ordered 48 probes from the n-terminal sequence amino acid range 20 through 26. (Tr. 5, 99-100). This set of probes was partially degenerate; a fully degenerate set would have had 192 probes. (Tr. 5, 99-101). As of September, 1981, Lin was not sure whether 192 probes could be used to screen a genomic library. (Tr. 5, 102).

On February 5, 1982, Lin designed two other sets of probes which were not fully degenerate from amino acids 20 through 26 of the n-terminal sequence. (Tr. 5, 107).

Dr. Lin testified that prior to January 12, 1982 he ordered a fully degenerate set of 32 probes from amino acid region 18 through 22. (Tr. 5, 108; DX 628). He also testified these probes were "purified" on January 12, 1982. (Tr. 6, 8). The document which Amgen relies on to support this testimony, however, bears the date March, 1982. (DX 628; Tr. 6, 10). Lin testified that the lawyers mistakenly relied on this document which had the probes from this amino acid region and could not explain why the March, 1982 date was on the document. (Tr. 6, 19). These probes did not work properly. (Tr. 5, 121).

On March 22, 1982, Lin designed a partially degenerate set of eight probes from amino acid range 20-26 out of a possible 192 probes. (Tr. 5, 115). On July 17, 1982, he ordered one probe from amino acid range 19 to 25. (Tr. 5, 116). At approximately the same time, he ordered another partially degenerate set of probes from amino acid range 20 to 26. (Tr. 6, 15).

The first time Lin remembers using a fully degenerate probe to screen a library was in May, 1982. (Tr. 4, 55-56; 5, 61). Lin encountered problems in using oligonucleotide probes with a large number of nucleotides because these probes created "high backgrounds" on the filters where the screening is done. (Tr. 4, 56).

On June 3, 1982, Dr. Eugene Goldwasser, Amgen's consultant on the EPO project, sent Amgen 15 fragments of human urinary EPO. (Tr. 4, 57; 5, 40). To obtain these fragments, the purified EPO had been cleaved (or "digested") by the enzyme trypsin and then separated by a high pressure liquid chromatography procedure. (Tr. 4, 57; PX 63-21). Fragments made this way are called tryptic fragments. (Tr. 4, 59). Goldwasser cleaved the protein into smaller pieces to make it easier to obtain the amino acid sequences information from internal fragments of the EPO gene (Tr. 4, 57). Probes can then be designed from these internal amino acids sequences. It was important to get these internal sequences because the probes from the n-terminus had been unsuccessful.

Lin was not successful in obtaining successful probes from any of these fifteen fragments which identified the EPO gene. (Tr. 4, 58). By the end of 1982, Lin felt like a "lonesome soldier", because the company felt so frustrated with the EPO project and felt it was dead; no one at the company wanted to touch it. (Tr. 6, 34).

On April 26, 1983, Lin ordered a fully degenerate set of probes from amino acid sequence region 62 to 67. (Tr. 5, 117-118). Because there was an error in the sequence information for position 67, the probes did not work. (Tr. 6, 25).

Lin obtained additional tryptic EPO fragments from Goldwasser at the end of August, 1983. (Tr. 4, 59). Dr. Por Lai's department sequenced the fragments provided by Dr. Goldwasser. (Tr. 5, 43). The probes designed from these fragments were successful. (Tr. 4, 59). Lin designed three sets of "fully degenerate" probes, called EpV, EPO-17 , and EpQ, in September, 1983, and ordered them from a branch of Amgen in Boulder, Colorado which synthesizes oligonucleotide probes. (Tr. 4, 63; PX 63-29; PX 63-31). Each set of probes had 128 different sequences. (Tr. 4, 63-64). The EpV probes, ordered on September 2, 1983, were from amino acid region 46-52. (Tr. 5, 122-123). The EpQ probes, ordered on September 24, 1983, were from region 86-91. (Tr. 5, 123). EPO-17 covered the amino acid sequence region 18-23. (Tr. 6, 15-16). (A chart, marked DX 750, outlines all the probes ordered by Dr. Lin.)

Lin used the following method to clone the gene. First, he "plated out" the genomic library in "phage," which is a virus that infects bacteria, and fixed the DNA onto a filter. (Tr. 4, 60). He obtained the genomic library from Dr. Maniatis. (Tr. 6, 27). He then screened or "probed" the library by exposing the filter to the EpV set of oligonucleotide probes to determine which portions of the DNA the probes would "hybridize" or bind with. (Tr. 4, 60). The probes carried a radioisotope tag

which would signal hybridization. (Tr. 4, 60). After hybridization, Lin washed off the nonspecific hybridization signal, and took an x-ray of the filter. The area of hybridization showed up as a black spot in the film. (Tr. 4, 60). Then, Lin cooked the filter to remove the probes, and applied the EpQ set of probes taken from a different region of the EPO internal amino acid sequence.[2] (Tr. 4, 60-61, 65). He followed the same hybridization and x-ray procedure. (Tr. 4, 61). He then matched up the two films; where the black spots were the same, there was a good chance the EPO gene had been isolated. (Tr. 4, 61). Lin then matched the dark spots on the film with the original plate that contained the phage and picked out the portions of the phage which corresponded to the spots. (Tr. 4, 61). Those portions contained the clones with the positive hybridization signals. (Tr. 4, 61). Then, Lin went through a rescreening and dilution process to make sure the phage did not contain contamination from a neighboring phage. (Tr. 4, 62).

This is how Dr. Lin isolated the EPO gene and pulled it out of the genomic library. (Tr. 5, 55). Dr. Lin believed that his cloning method was different from what people had done before, and was a scientific advance, because he used big 128-sequence complex mixtures of probes to screen a genomic library which is a more complex library than one made up of cDNA. (Tr. 5, 56, 59). He also believed that the use of 128 probes was a larger number than others had used to screen a genomic library. (Tr. 5, 95).

The successful cloning of the EPO gene took place in September or early October, 1983. (Tr. 4, 64-66; 5, 123-124). This was the first time that Lin ever designed, ordered and used two sets of probes, both fully degenerated, from two dif-

[2] Before using the EpQ set of probes, Lin had used the EPO-17 set of probes from the n-terminal sequence, which did not successfully hybridize with the EPO gene. (Tr. 4, 65).

ferent regions of the EPO gene to screen a genomic library. (Tr. 5, 91, 124). Amgen (someone other than Dr. Lin) sequenced the gene to confirm it was the EPO gene. (Tr. 4, 74).

In late October, 1983, Lin cloned the monkey cDNA EPO sequence. (Tr. 4, 72). On December 3, 1983, Lin also hybridized the human EPO gene to monkey EPO cDNA so that he could determine from an electron micrograph which area of the human DNA consisted of introns, and what the sizes of the exons and introns were. (Tr. 4, 68-72; PX 63-38).

Lin filed his first patent application on December 13, 1983. (Tr. 4, 74). Amgen issued a press release at about the same time. (Tr. 4, 76; PX 49). Amgen's successful cloning of the gene was reported in McGraw-Hill's *Biotechnology Newswatch*, dated January 2, 1984. (Tr. 4, 77).

By January 10, 1984, Amgen had expressed human EPO in human embryonic kidney cells called "293" cells and in COS cells, which are monkey kidney cells. (Tr. 4, 75-77; PX 63-39; PX 63-41). Someone other than Dr. Lin did the work with the mammalian expression system. (Tr. 5, 51-52). Lin was personally involved in the E. Coli expression of EPO. (Tr. 5, 52). On February 13 and 14, 1984, Amgen conducted experiments to show that the recombinant human EPO produced in the COS cell was biologically active. (Tr. 4, 80).

On February, 21, 1984, Lin filed his second patent application. (Tr. 4, 81).

From March 1-9, 1984, Amgen conducted an *in vivo* bioassay and determined that the recombinant EPO was biologically active. (Tr. 4, 82-83).

On March 15, 1984, Lin obtained the human full length EPO cDNA gene. (Tr. 4, 83; 5, 28).

On April 5, 1984, Lin specified the nucleotides necessary to synthesize a human EPO gene which could be used for expression in yeast cells. (Tr. 4, 84-85). When a gene is synthesized by chemical means, the introns are excluded, and

it is easier to manipulate the gene for expression in different organisms. (Tr. 4, 85).

By May 2, 1984, human rEPO had been expressed in CHO cells. (Tr. 4, 86). Jeff Browne and Ralph Smalling worked together on the EPO project team, which Lin continued to head through 1984, to develop a cell line in 1984. (Tr. 6, 66). In developing a cell line to express rEPO, Amgen used as starting material a mammalian host cell called CHO DHFR- (DuXB11) for transfection. (Tr. 6, 49; PX 2, Col. 26, l. 51). This host cell was from a cell line developed by Professor Lawrence Chasin at Columbia University who has no connection with Amgen. (Tr. 6, 49). After transfection, Amgen had a heterogeneous cell population, and used MTX amplification and limited dilution cloning to develop a production cell line. (Tr. 6, 55-56). A heterogeneous cell population is called a cell strain, and a homogeneous population developed from one single cell is called a cell line. (Tr. 6, 65, 74). A master cell bank is created from the cell line. (Tr. 6, 75). A cell strain cannot be used for production purposes, only a cell line. (Tr. 6, 98).

By August 27, 1984, five different sublines of human EPO-CHO ("huEPO-CHO") had been produced. (Tr. 6, 66; DX 336). Browne had chosen two of the lines, B11 30/50/100 and B11 50 for a radioimmunoassay. (DX 336). Joan Egrie reported to Lin in September, 1984 that she had studied the huEPO-CHO cell line B11 30/50/100 for EPO production. (Tr. 6, 70). She also conducted a radioimmunoassay ("RIA") and *in vivo* assay of the produced EPO. (DX 337). At that point, Amgen had narrowed its consideration of cell strains to the B11 30/50/100 host cell. (Tr. 6, 71). On September 19, 1984, Dr. Browne told Lin that amplification of huEPO-CHO cells with MTX was continuing, and he was "getting ready to create a master cell bank from cell line B11 30/50/100." (Tr. 6, 73; DX 295). The cell strain B11 30/50/100 was the CHO B11 cell trans-

formed with the human EPO gene and amplified through 30 nanomolar, 50 nanomolar and 100 nanomolar MTX. (Tr. 6, 93, 96; 10, 12). Nanomolar is a concentration measurement. (Tr. 6, 96). This strain was equivalent to B11 3,.1, which is a short-hand way of describing the amplification process from 30 nanomolar MTX amplification through 100 nanomolar MTX amplification. (Tr. 6, 99; 10, 12).

By October 19, 1984, Dr. Browne had written a memorandum to Kirin-Amgen which identified Amgen's "current process for the production of EPO" from the "production cell line, CHO B11 3,.1." (DX 347). On October 31, 1984, Amgen decided that it would start making a master cell bank on November 26, 1984. (Tr. 6, 84; DX 291). By September, 1984, Amgen had decided that the best way to express EPO was from mammalian cells, not yeast cells or E. Coli bacterial cells. (Tr. 6, 83, 106). On November 30, 1984, Browne distributed to Lin, among others, the November 28 Product Development Team ("PDT") meeting minutes which stated: "This first product will be EPO secreted from a clone of the CHO cell line B11-3,.1." (Tr. 6, 85; DX 349).

As of November 30, 1984, Amgen had made the decision that a clone from CHO cell strain B11 3,.1 would be used to produce EPO, and Dr. Lin knew this. (Tr. 6, 84-89). On December 3, 1984, Dr. D. Vapnek, research director at Amgen, wrote a memorandum to Amgen's general counsel, R. Weist, stating that the EPO-producing CHO cell line designated CHO B11 3,.1 was available for transfer. (DX 350; Tr. 6, 90). The patent does not identify by name any clones of CHO B11 3,.1. (Tr. 6, 103).

Lin filed his third application for a patent on September 28, 1984. (Tr. 5, 6). The fourth application was filed on November 30, 1984. (Tr. 5, 6).

In September, 1984, Lin deposited with the American Type Culture Collection ("ATCC") in Bethesda, Maryland, the best

E. Coli cell strain used for the production of EPO, but without the EPO gene in the cells. (Tr. 6, 105). He also made a deposit of the best yeast cell strain. (Tr. 6, 106). These cell strains did not contain the EPO gene. (Tr. 6, 108). No mammalian host cell strain or line, including any CHO cell, was ever deposited with the ATCC. (Tr. 6, 107, 118).

In the February 25-March 6, 1985 issue of *Nature* magazine, Amgen had an advertisement that it was selling recombinant human EPO to the research community for research use. (Tr. 5, 31). In November, 1985, Amgen filed an Investigative New Drugs ("IND") application with the Food and Drug Administration ("FDA") asking for approval to try out EPO on renal failure patients. (Tr. 5, 32). Amgen received approval in December, 1985 for the initial stages of this clinical experiment, and nineteen months later received FDA approval for the last two stages. (Tr. 5, 32).

On October 20, 1987, seven days before the patent issued, Lin deposited an E. Coli cell transfected with the monkey EPO clone, and the human EPO clone in "lambda phage," with the ATCC. (Tr. 5, 7). Lambda phage is the tiniest living creature that will infect bacteria. (Tr. 5, 7). The monkey and EPO clones were available in 1984. (Tr. 6, 113).

In November, 1987, Amgen filed a Product License Application ("PLA"), asking for FDA approval to market EPO for the treatment of renal anemia patients, and on June 1, 1989, the FDA granted this approval. (Tr. 5, 33).

c. Genetics Institute.

In late spring, 1981, Dr. Edward Fritsch became a consultant to GI. (Tr. 25, 130). In November or December, 1981, Dr. Maniatis, a founder of GI, talked to Fritsch about joining GI, and he accepted that offer before Christmas, 1981. (Tr. 25, 133). Dr. Fritsch arrived at GI in April, 1982, and became the

EPO project leader until 1984. (Tr. 22, 50). He resumed this project leadership in late 1985 until 1986. (Tr. 22, 50).

Fritsch received a bachelor's degree in biology from MIT; received a PhD from the University of Wisconsin in 1977 in the field of molecular biology; did postdoctoral work at the University of Southern California in 1977 and 1978; did additional postdoctoral working molecular cloning at Cal Tech during the years 1978 to 1980; and was an assistant professor at Michigan State University teaching molecular biology from 1980 to 1982. (Tr. 22, 49). While at Cal Tech, he was one of the postdoctoral fellows working with Dr. Maniatis on the development of a complete human genomic DNA library in early 1978. (Tr. 25, 42). He also taught molecular cloning at Cold Spring Harbor, a private research institute, and co-authored with Dr. Maniatis and another scientist a manual on molecular cloning. (Tr. 25, 59-60).

Maniatis and Fritsch used the library to isolate the human globin gene cluster. (Tr. 25, 42). Globin genes are the genes for two proteins that are present in hemoglobin, which is the molecule involved in transporting oxygen from the lungs to the rest of the body tissue and carbon dioxide back to the lungs. (Tr. 25, 52). To clone this gene, Fritsch used one extremely long probe made from an already existing cDNA clone to screen the genomic library. (Tr. 25, 53).

In 1981, Fritsch discussed with Maniatis the possibility of working on the EPO project. Maniatis told Fritsch that GI had some amino acid sequence information from Dr. Rodney Hewick concerning the EPO gene. (Tr. 25, 133). They also discussed that there was no known tissue source available for EPO. (Tr. 25, 133). Dr. Fritsch then considered how one might approach the cloning of the EPO gene based on having some available sequence information, and the idea of using two fully degenerate oligonucleotide probes to screen a genomic library came to mind. (Tr. 25, 134).

Dr. Fritsch was aware of a formula to compute the number of clones that will hybridize with a probe or a set of probes in a given library. (Tr. 25, 121-124). There was nothing novel about this formula. (Tr. 25, 139). In November or December, 1981, in connection with the EPO project, he used this formula and made computations in the abstract assuming a reasonable set of sequences for two probes to see if in principle this approach of combining both probes could lead to a very small number of positive EPO clones. (Tr. 25, 126, 134). He assumed one 14-mer probe of 48-fold degeneracy, and another of similar length and degeneracy. (Tr. 25, 134). He concluded that the use of fully degenerate probes in combination to screen a genomic library would allow one to come down to a reasonably small number of unique positives for the purpose of identifying the particular gene of interest and told Dr. Maniatis of this idea before Christmas, 1981. (Tr. 25, 126, 135). When he conceived of this idea, he had never personally used oligonucleotide probes before. (Tr. 25, 138). He considered the concept of applying the two different probes in combination to find within a genomic library the sequences that would hybridize to both to be novel. (Tr. 25, 139). Dr. Maniatis also considered the strategy to be novel because no one had thought of going directly from the amino acid sequence of protein to a genomic clone. (Tr. 36, 58).

In August, 1982, Dr. Fritsch prepared a document to describe the two cloning approaches which GI would undertake. (PX 37A). The first approach primarily relied on currently available n-terminal sequence information for EPO from Dr. Hewick. (Tr. 26, 11). The second cloning approach involved obtaining additional erythropoietin and then using additional sequence information. (Tr. 26, 11). GI made a decision in August or September 1982 to follow the first approach, and focus its efforts on getting the EPO gene on the basis of the n-terminal sequence. (Tr. 26, 16). After discussions with Dr.

Miyake beginning in June, 1982, GI initially decided not to take the second approach because it could not afford the terms demanded by Dr. Miyake for the EPO. (Tr. 26, 18).

When Hewick gave Fritsch the n-terminal sequence information in early 1982, he did not know the amino acids at positions 3 and 7, and was unsure of the amino acid at position 27. (Tr. 26, 16). Based on the n-terminal information, in September, 1982, Fritsch designed three sets of fully degenerate probes from amino acids 18 through 26. (Tr. 26, 21-23). The EPO E probes were from amino acids 22 through 26; the EPO D probes were from 18 through 22; and the EPO ABC probes were from 18 through 24. (Tr. 26, 24-25). Fritsch later found out that the amino acid at position 24 was wrong. (Tr. 26, 22). Therefore, one of the sets of probes, EPO E, had an error in the middle of it. (Tr. 26, 28). On October 13, 1982, Fritsch began to screen the genomic library with the EPO ABC set of probes, and on October 20, 1982, rescreened with a second EPO E set. (Tr. 26, 32-33). Fritsch was unsuccessful in isolating the gene because the second probe had incorrect amino acid information. (Tr. 26, 36).

On January 5, 1983, Fritsch again probed the genomic library using all three sets of probes, again unsuccessfully. (Tr. 26, 48). In February, 1983, and April, 1983, a third screen and fourth screen of the genomic library were conducted using two of the probes, including the E probe which had the inaccurate coding information. (Tr. 26, 51-54). None of the screens was successful, in retrospect, because the E probe had an error in the middle of it. (Tr. 26, 56).

By late April or May, 1983, GI began to search for additional EPO protein. (Tr. 26, 57). In May, 1983, Fritsch contacted Dr. Arthur Sytkowski, an investigator at Children's Hospital who had indicated that he had some urinary EPO which GI proposed to jointly purify; no agreement was reached. (Tr. 26, 58-60). Fritsch also contacted Dr. Judith Sherwood because

she had a cell line that was producing EPO but, after testing the cell line, Fritsch concluded in November/December, 1983 that there was not enough EPO produced from Dr. Sherwood's cell line to justify an effort to purify it. (Tr. 26, 60-64). Sherwood did give GI some EPO which she had received from Dr. Goldwasser but that was not sufficient to obtain useful amino acid sequence information. (Tr. 26, 64-66).

As a result of the lack of success with the first four screens, Dr. Fritsch decided to design probes from a different region of the n-terminal sequence between residues 14 and 19. (Tr. 26, 67-68). This region was highly degenerate and a fully degenerate set would have required 576 probes. (Tr. 26, 68). Such a large number of probes often increases the background noise, and makes it harder to read hybridization signals. (Tr. 26, 69). Fritsch designed a subset of 256 probes which, based on the codon usage rules, had the highest probability of containing the correct sequence. (Tr. 26, 71-72). During July and August, 1983, this subset was used with the fully degenerate EPO ABC set of probes to conduct four screens of genomic libraries, again unsuccessfully, because again in retrospect, one of the codons was predicted incorrectly. (Tr. 26, 79-80). In March or April, 1984, Fritsch ordered a fully degenerate set from the region 15 through 19, but never used this probe because GI was close to getting additional purified urinary EPO from Dr. Miyake. (Tr. 26, 81-82).

In April, 1984, GI received purified EPO from Dr. Miyake. (Tr. 15, 66). Dr. Hewick provided sequence information from two tryptic fragments identified as T-35 and T-30. (Tr. 26, 89-91). Dr. Fritsch designed one set of fully degenerate probes from T30 which covered the amino acid region 145 through 150. (Tr. 26, 94-95). He also designed three sets of fully degenerate probes from the tryptic fragment T-35 which covered region 46 through 52. (Tr. 26, 92). Fragment T-35 covered the same region as that used by Dr. Lin to design one of the probes he used to successfully isolate the EPO gene. (Tr. 26, 91).

On May 30, 1984, the genomic library for isolating the EPO gene was plated and hybridized using two sets of probes, both fully degenerate, from different regions of the amino acid sequence. (Tr. 26, 96-98). This process resulted in the identification of two clones in July, 1984, both of which were the full gene for EPO. (Tr. 26, 100-102). This was the first time that GI used two sets of fully degenerate probes based on the correct amino acid sequence for EPO. (Tr. 31, 46). Also, Dr. Fritsch used a hybridization solution called TMAC, which had not been used by Dr. Lin when he cloned the EPO gene. (Tr. 7, 101; 26, 86).

The positive clones were then used to construct a single long probe to screen a cDNA library constructed from human fetal liver, and on August 6, 1984, cDNA clones were successfully isolated. (Tr. 26, 104-106). GI transfected a CHO cell with a cDNA clone for EPO; this was the expression system with which GI was most familiar. (Tr. 26, 107).

GI described its successful cloning of the EPO gene in an article published in the February, 1985 issue of *Nature* magazine. (PX 579). On January 3, 1985, GI filed a patent application (the "'285 application") claiming a purified and isolated DNA sequence, vectors into which such a sequence has been inserted, and transfected host cells.

In a related area, GI was successful in 1983 in cloning a portion of the Factor VIII protein which is important in causing blood to coagulate. On September 20, 1983, GI successfully cloned a portion of the Factor VIII gene using two sets of probes — one fully degenerate and other a guessmer — to screen a genomic library. (Tr. 26, 83, 85). A patent issued to Dr. Fritsch and Dr. John Toole on Factor VIII as a result of a patent application filed on October 28, 1983. (DX 7).

d. Other Biotechnology Companies.

Prior to December, 1983, other biotechnology companies had tried to clone the EPO gene. One company, Biogen, began

its EPO project at the end of 1981, and continued it as a full-scale project until March, 1985, when the project was "officially terminated." (Tr. 8, 21-22). Biogen invested approximately $4,000,000 to $6,000,000 in that project. (Tr. 8, 31).

Two major strategies were followed at Biogen to clone the EPO gene. One strategy, which biogen scientists had used very successfully in cloning the interferon gene, was to identify both a good source of erythropoietin messenger RNA and another source that was poor in that particular messenger RNA and then to use what is known as "competition" to purify the messenger RNA for EPO. (Tr. 8, 23). cDNA libraries would then be constructed as the means to obtain and isolate the gene. (Tr. 8, 23-24).

In the beginning, rats made anemic, or hypoxic, by treatment with chemicals were used as sources for mRNA for erythropoietin. (Tr. 8, 24). At about the same time, similar experiments were being carried out in Biogen's Cambridge laboratories on baboons that were made anemic by phenylhydrazine so that they would produce more EPO. (Tr. 8, 24; 27, 23-24). Oligonucleotide probes based on the n-terminal amino acid sequence of human EPO were used to screen the cDNA library prepared from the kidney tissue of the phenylhydrazine-treated baboons. (Tr. 27, 27-28).

The second strategy used at Biogen was to obtain a source of the EPO protein, the hormone itself; to find the sequence information for that protein; to design oligonucleotide probes that corresponded to that sequence; and then to use those oligonucleotide probes to screen cDNA libraries. (Tr. 8, 25). To obtain the erythropoietin, Biogen looked around for people who might be able to supply it and started collecting thousands of liters of urine from anemic humans in an attempt to purify the gene itself. (*Id.*). Requests made by Biogen to Dr. Goldwasser and the National Institutes of Health in late 1981 and early

1982 for high purity EPO were turned down. (Tr. 37, 60-61; DX 390; DX 910). Also, Biogen's own effort to purify EPO from the urine samples of anemia patients was not successful in terms of providing pure EPO. (Tr. 8, 41).

The only known sequence for EPO that Biogen had up until 1983 was the sequence of the n-terminal region obtained by Dr. Hewick at Cal Tech. (Tr. 8, 28-29). Biogen had only a single segment of the sequence which was presented by Dr. Goldwasser at a meeting in 1981. (Tr, 27, 48). Two Biogen scientists were present at that meeting and they copied it down as best they could, but there were gaps at positions 19, 20 and 22. (Tr. 27, 48-49). There were also errors in the sequence at residues 7 and 24 which were not discovered until much later in early 1983. (Tr. 27, 50). Dr. Julian Davies, who was director of research and subsequently also president of Biogen in Geneva, Switzerland from 1980-1985, believed that the errors were "clearly one of the factors which mitigated again successful cloning," although he did not know whether the amount of sequence information would have been sufficient in any event. (Tr. 8, 18-19, 29).

The oligonucleotide probing approach used at Biogen was to employ two sets of probes — in general, fully degenerate — to screen the libraries that contained the gene of interest. (Tr. 27, 22). Biogen did not succeed in isolating the baboon cDNA gene encoding for EPO using this mixed oligonucleotide approach. (Tr. 27, 53). Dr. Richard Flavell, who was president of Biogen's Cambridge, Massachusetts facility from 1982 to 1988, said "[w]e concluded at the end of '82, beginning of '83, that there was something wrong" with the sequence and therefore that "our failure to get the clones was that somehow or other our probes were wrong." (Tr. 27, 18-20, 54).

When it heard rumors that the sequence might be incorrect, Biogen tried in 1983 to obtain sequence information from crude human urinary EPO received from Dr. Zanjani. (Tr. 27,

55). Biogen was unable to obtain purified EPO from that shipment. (Tr. 27, 56). At the end of 1983, Biogen received another sample of EPO from Dr. Suyama at the Green Cross Company in Japan. (Tr. 27, 64). From that sample, Biogen was able to obtain n-terminal sequence information, but the sequence determined by Biogen scientists contained an error at position 24. (Tr. 27, 65, 67). A second shipment of EPO was obtained from Green Cross in January or February of 1984. (Tr. 27, 67). The material from that shipment was fragmented and sequenced. (Tr. 27, 67-68). As a result of that sequencing effort, Biogen was able to obtain a new internal sequence of the first nine residues useful for making a "nice" 20-mer probe or 128-fold redundancy or degeneracy. (Tr. 27, 68-69).

Biogen, at some point, began to use a genomic library as the library for isolating the EPO gene. (Tr. 27, 75). It decided to use genomic libraries for isolating the gene for Factor VIII in 1983, and by the end of that year or the beginning of 1984, it began to use the genomic library on the EPO project. (Tr. 27, 75-76).

Biogen eventually succeeded in cloning the EPO gene in mid-1985, after the EPO project had been officially terminated and after the full sequence for the EPO gene had been disclosed in a publication by GI in the February, 1985 issue of *Nature* magazine. (Tr. 8, 30, 32). According to Dr. Flavell, the limiting factor in Biogen's effort to clone the gene was not having an adequate amount of protein sequence from which to derive good probes. (Tr. 27, 97). He said erythropoietin was a "rather rare commodity" and the major person who had that material was Dr. Goldwasser. (Tr. 27, 97-98).

Another biotechnology company that attempted to clone the EPO gene was Genentech. (Tr. 7, 12). Genentech's EPO project began in 1981, and extended over a period of 1 and ½ years, until the end of 1982. (Tr. 7, 12, 17). At that time, Genentech abandoned the project because it heard the rumor

that Amgen had succeeded in cloning the gene, which later proved to be untrue. (Tr. 7, 17).

e. Prior Art.

During the period from 1980 through 1983, the technology in the field of cloning advanced very quickly. (Tr. 8, 62-63). During that time period, various publications were issued about cloning techniques and cloning efforts, which added incrementally to the information available in that field. (Tr. 8, 63).

First, at the end of December, 1980 or the beginning of 1981, Dr. Wallace and others published an article which was the "seminal paper" on using probes. (Tr. 27, 101-102; DX 200). In that experiment, Dr. Wallace used eight oligonucleotide probes, which were *not* fully redundant, to hybridize with cloned rabbit betaglobin DNA sequences. (Tr. 27, 102, 104-105; DX 200). The article was useful because it showed that correct probes in a mixture of both correct and incorrect probes could distinguish the clone by hybridizing with it, whereas the incorrect probes would not. (Tr. 27, 104). No library was screened in the experiment, and the article did not mention using probes from different regions. (Tr. 27, 105-106).

In November, 1981, a second article was published which had been submitted by Dr. Suggs and others in June of that year. (Tr. 27, 107; DX 189). That paper went "to the logical next step from what [Dr.] Wallace did, which [was] to use mixed oligonucleotide probes to screen an actual library." (Tr. 27, 109). In the experiment, a cDNA library was used as well as two sets of probes. (*Id.*). The first set of probes used to screen the library was a 15-mer probe of 16-fold redundancy, and the second set was an 11-mer probe of 8-fold redundancy. (Tr. 27, 109-110). Only the second set of probes used was fully degenerate. (Tr. 27, 110).

Next, in September, 1982, an article submitted in June, 1982 by Dr. Woods was published. (Tr. 27, 110-111; DX 204).

Woods' article provided additional information because two fully degenerate sets of probes were used to screen a cDNA library. (Tr. 27, 111-112). The first set of probes was 32-fold degenerate, and the second was 48-fold degenerate. (Tr. 27, 112). The experiment showed that one could isolate a cDNA clone from a complex cDNA library using two sets of fully redundant probes. (*Id.*). Also, the quality of screening was "considerably better" than before, with a much better signal-to-noise ratio so that the positive looks very positive and the negative looks very negative. (Tr. 27, 112, 114).

In 1982, an abstract by Reilly also was published in a journal called *DNA*. (Tr. 27, 116; DX 183). The abstract dealt with the cloning of a gene from a genomic library. (Tr. 27, 116). Two probes of single redundancy were used to screen a genomic library of mouse DNA for the gene for transfer RNA. (*Id.*). The probes were from separate regions of the tRNA sequence, one being 15 bases long and the other being 19 bases long. (Tr. 27, 117, 119). The abstract showed that what had been learned with respect to cDNA could be applied to genomic DNA. (Tr. 27, 118).

In April, 1982, another abstract by Seki, et al., was published. (Tr. 27, 119; DX 185). In that experiment, a genomic library was screened using two sets of fully degenerate probes. (Tr. 27, 120). The first set of probes was a 16-mer probe of 48-fold redundancy, and the second was a 14-mer probe of 16-fold redundancy. (Tr. 27, 121). They were derived from different regions of the protein relatively close to one another. (Tr. 27, 124).

Whether Seki and his colleagues were successful in isolating the gene they wanted cannot be determined from the abstract because they had not at that point sequenced the material which had hybridized to the probes. (Tr. 28, 3). The abstract added to the prior publications by showing that what had been done previously for the cDNAs using two sets of redundant probes could also be done for genomic DNA. (Tr. 27, 121).

In September, 1983, an article submitted by Whitehead and others in May, 1983 was published. (Tr. 28, 4; DX 203). That experiment involved the use of a very complex single 23-mer probe of 384-fold degeneracy to screen a human liver cDNA library for the C4 gamma gene. (Tr. 28, 4-5, 7; DX 203). The set of probes used was fully degenerate. (Tr. 28, 6). Earlier, in April, 1983, Derek Woods, one of the authors of the article, presented this work at a meeting. (*Id.*). He indicated at the meeting that 384 probes had been used, and that he had found the gene he was looking for. (*Id.*). The abstract handed out at the meeting stated: "A C4 cDNA clone was isolated from the human adult liver cDNA library using a synthetic oligonucleotide mixture containing all 384 possible sequences coding for amino acids 14-21 of the C4 [gamma] chain." (DX 203A).

On October 28, 1983, Drs. Toole and Fritsch filed an application for a patent, which was eventually issued on July 12, 1988. (DX 7). The patent covered the screening of a genomic library with two probes to isolate the porcine Factor VIII gene. (Tr. 28, 10). The first probe was not fully degenerate, but was a long probe or guessmer 45 nucleotides long of 4-fold redundancy. (Tr. 28, 10-11, 14). The second probe was a 15-mer fully degenerate probe of 16-fold redundancy. (Tr. 28, 12). The Toole/Fritsch patent set forth information in addition to the prior published literature on probing and cloning in that it described in great detail the use of redundant probes to *successfully* isolate a genomic clone. (Tr. 28, 13).

The '008 patent application filed on December 13, 1983 described the screening of both a cDNA and genomic library to successfully isolate the EPO gene. (Tr. 28, 27-28). The patent reported that one set of 128 fully degenerate probes was used to screen the monkey cDNA library. (Tr. 28, 24-27). Dr. Lin testified that one partially degenerate set of probes of 16-fold redundancy was used on the monkey cDNA library. (Tr. 28, 24-25). Two sets of fully degenerate probes, each of 128-fold redundancy, were used to screen the genomic library. (Tr. 28, 27-29).

Dr. Flavell testified that these publications show a "continuum" or "gradual evolution" from the "quantum leap" made by Dr. Wallace in the first publication to use oligonucleotides. (Tr. 28, 23).

VII. PURIFICATION OF EPO

a. The Miyake purification procedure.

Prior to 1980, EPO was obtained by purifying the urine of patients suffering from aplastic anemia; that kind of urine was in short supply. (Goldwasser Dep. Tr. Vol. II 48-49). During the period from 1974 to 1976, Dr. Takaji Miyake, working with Dr. Goldwasser, developed a procedure for purifying this urinary EPO ("uEPO") in the laboratory of Dr. Goldwasser at the University of Chicago. (Goldwasser Dep. Tr. Vol. II 49-50; Miyake Dep. Tr. 43). Miyake had begun working on the purification of EPO in about 1964. (Miyake Dep. Tr. 27). He believed that this procedure provided a homogeneous pure EPO product in the 1976 and 1977 time frame. (Miyake Dep. Tr. 159).

Dr. Miyake, Dr. Goldwasser and Charles K. H. Kung published this seven-step procedure in an article entitled "Purification of Human Erythropoietin" in the *Journal of Biological Chemistry* in 1977. (PX 528) ("*Miyake et al.*"). The authors reported: "Human erythropoietin, derived from urine of patients with aplastic anemia, has been purified to apparent homogeneity. The seven-step procedure which included ion exchange chromatography, ethanol precipitation, gel filtration, and adsorption chromatography, yielded a preparation with a potency of 70,400 units/mg of protein in 21% yield." (PX 528). The article also reported that Fractions II and IIIA had a "mean potency of 82,720 U/A", and that human EPO has a "minimal potency of 70,400 units/mg". (PX 528). Table IV stated that Fraction II had a potency of 128,620 U/A. (PX 528).

Further, the article reported the apparent molecular weight determined by SDS-gel electrophoresis to be 39,000 daltons. (PX 528, p. 5563).

A brief general discussion of purification techniques is needed to understand Miyake's procedures for purifying EPO. Chromatography was one of the purification techniques used by Miyake. In chromatography, a liquid sample containing a mixture of proteins is poured into the top of a narrow glass or metal cylindrical container, called a column, containing finely divided solid or small particles of beads. With the addition of a buffer solution, the proteins migrate down the column at different rates depending on the physiochemical properties of each particular protein. The proteins are then "eluted" or washed off, and collected into tubes at the bottom of the column. The protein sample collected in each of the these tubes is called a "fraction." (Tr. 17, 54-57).

There are various types of chromatographic columns used for the separation and isolation of glycoproteins. Chromatographic separations are accomplished by taking advantage of differing physiochemical properties, such as molecular size, solubility, electrical charge, affinity for other materials (adsorption) or hydrophobicity (the water-hating quality of a molecule). One chromatography column is called an ion-exchange column and separates proteins based on electrical charge density. (Tr. 17, 62-63). Another kind uses hydroxylapatite in the column which separates proteins by their adsorption properties; molecules with certain properties (for example, with different numbers of hydroxyl groups) are held in the column, while molecules without these properties are eluted off. (Tr. 17, 65-66, 88-89).

Miyake measured the specific activity of the fractions of urinary EPO ("uEPO"). Specific activity for EPO is usually measured in international units per absorbance units at wavelength A280. An international unit ("IU") is a unit to

measure the potency of a substance. An "absorbance unit" ("AU") is the approximate amount of light that is absorbed at a given wavelength, and can be expressed in milligrams (mg) of protein per milliliter (ml) of total protein concentration. (Recny Dep. Tr. 91). The measurement of specific activity can be specified as IU/AU or u/mg. To convert specific activity from u/mg to IU/AU, u/mg is divided by an extinction coefficient. (Tr. 22, 93-95). Fritsch used an extinction coefficient of 1.31. (Tr. 23, 51). Miyake believed the extinction coefficient was .851. (Tr. 24, 167).

The Miyake procedure was the standard procedure for obtaining high purity EPO at least through 1981. (Tr. 37, 42). The scientific community believed that EPO purified by the Miyake method was homogeneous and had a specific activity of 82,720 IU/AU or 70,400 u/mg. (Tr. 14, 95; DX 220, 324, 213, 326). Dr. Lin reported in his patent that the seven-step Miyake procedure yielded "a pure erythropoietin preparation with a potency of 70,400 units/mg of protein in 21% yield." (PX 2, Col. 7, 11. 29-35). Moreover, in one of the articles cited by Amgen entitled "Purification of Erythropoietin from Human Urine and Anemic Sheep Plasma by High Performance Liquid Chromatography," which was published in 1981 in *Blood*, the Journal of the American Society of Hematology, the authors stated: "Erythropoietin (Ep) has now been purified to homogeneity (Miyake et al; JBC 252: 5558, 1977)." (PX 545). When Dr. Thomas Strickland of Amgen attempted in 1984 to purify EPO using a modified Goldwasser procedure, he did not use a kind of chromatography called reverse phase high pressure (or high performance) liquid chromatography ("RP-HPLC") as a purification step, although he was familiar with that technique, because he believed the uEPO purified by the Goldwasser procedure was "pretty close to pure" and of "adequate purity" for his purposes. (Tr. 14, 67).

b. Dr. Rodney Hewick.

Dr. Rodney Hewick arrived at GI on September 1, 1981 to become GI's senior protein chemist. (Tr. 15, 36). Prior to joining GI, Dr. Hewick worked at Cal Tech, where he was one of the inventors of a device known as the "gas phase sequenator." (Tr. 10, 123). At Cal Tech, he used the sequenator on EPO received from Dr. Goldwasser's laboratory to determine the amino acid sequence for the first 26 residues from the n-terminus of the EPO gene. (Tr. 10, 130-31; 11, 23). As noted earlier, some of this information turned out to be incorrect. (Tr. 11, 22-23).

In early 1984, GI sought EPO from Dr. Miyake to obtain additional sequence information to construct probes. Dr. Hewick received four shipments of EPO from Dr. Miyake in April, May, July and November, 1984. (Tr. 11, 49-50). Miyake believed that the first and third shipment of samples provided to GI were of the same purity as the 1976 samples he had prepared with Dr. Goldwasser. (Miyake Dep. Tr. 338, 343-44).

When Hewick received the first sample from Dr. Miyake on April 23, 1984, he subjected it to SDS-PAGE analysis. (Tr. 11, 58; 15, 67). SDS-PAGE electrophoresis is another technique to isolate and purify proteins according to molecular weight. A mixture of proteins, which are stained, is poured into a gel; the proteins migrate through the gel, and separate solely according to size. The resting position of a particular protein is marked by a band resulting from the stain. Thus, a mixture of several different proteins with different molecular weights will result in different bands, somewhat akin to a ladder in appearance, with the different rungs indicating proteins of different weight. (Tr. 17, 71-77; 11, 54-55). This ladder is compared to the molecular weight of a known protein which is placed in a marker lane. Using SDS-PAGE analysis, Dr. Miyake had determined that the molecular weight of EPO is 39,000 daltons.

When he examined the SDS-PAGE gel from the first Miyake shipment, Dr. Hewick saw that there were bands other than those he thought to be EPO. (Tr. 15, 74). He then ran the sample on the RP-HPLC, and saw a series of peaks on the chromatogram. (Tr. 15, 79).

RP-HPLC is a form of chromatography which separates proteins based upon hydrophobicity, or water-hating qualities. As the proteins elute from the column according to their different hydrophobic characteristics, an optical detector, known as a spectrophotometer, at the end of the RP-HPLC column measures the intensity of light at a given wavelength that passes through the solution as it flows off the RP-HPLC column. The spectrophotometer gives an absorbance value that measures the amount of light which is actually absorbed by components in the protein. Typically, for proteins, a wavelength of A280 is used; at that wavelength, the absorbing components in proteins are the amino acids, tryptophan and tyrosine. (Tr. 11, 73-75). Protein chemists also use traces which reflect absorbance at a wavelength of 214 nm. (Tr. 15, 50, 59, 76). A strip chart recorder signal is plotted in a line or "trace" form, called a chromatogram. As the protein elutes off the chromatographic column according to its hydrophobic characteristics, at designated times, the spectrophotometer will record the absorbance at A280, and a peak will appear. (Tr. 11, 75-82). A chromatogram will not measure the relative mass of a protein coming off a column, but rather its relative absorbance at 280 nm. (Tr. 11, 75-82). If there are different proteins in a mixture, different peaks will appear on the chromatogram. If the mixture is homogeneous, only one peak will occur.

RP-HPLC was not available in 1977 when Miyake developed his procedure to purify EPO. By 1983, it was used by the scientific community to separate glycoproteins. Dr. Goldwasser began to use RP-HPLC in about 1982, and used it for checking the purity of previously prepared materials, including EPO.

(Goldwasser Dep. Tr. Vol. II 39). Dr. John G. Pierce, Amgen's expert, used RP-HPLC to successfully purify the glycoproteins he was working with in 1982 and 1983. (Tr. 18, 20-23). Two published abstracts demonstrate the use of RP-HPLC to purify EPO from biological fluids in 1981 through 1982. (PX 545, 543). RP-HPLC was used to separate the human thyroid-stimulating hormone, which is a glycoprotein, in 1983. (PX 540).

Hewick conducted a second run of the Miyake material on RP-HPLC loading four to five times the amount loaded during the first run. (Tr. 15, 87-88). He saw peaks and plateaus on the 280 and 214 traces. (Tr. 15, 88-89). A plateau in a trace, as opposed to a peak, reflects heterogeneity; a large number of trace amounts of proteins might produce a plateau. (Tr. 15, 90-91). Altogether, Hewick conducted five runs, and all the chromatographs revealed a small peak appearing at 17 to 18 minutes, a large plateau, and a larger peak appearing at 36 to 38 minutes. (Tr. 15, 106-108). He sequenced the fractions from the fifth run on the gas phase sequenator. (Tr. 145, 110-119). The sequences indicated that only the fraction corresponding to the large peak appearing at 36 to 38 minutes was EPO. (Tr. 15, 116-117).

Hewick subjected the EPO fraction from run 5 to tryptic digestion, and then separated the fragments on RP-HPLC. (Tr. 15, 120-122). The fragments produced a good tryptic map, indicating areas of high 280 absorbance where the tryptic fragments contained the amino acids tyrosine and tryptophan, which facilitates the designing of probes. (Tr. 15, 123-26). Hewick chose two of these fragments, T-30 and T-35, for sequencing and delivery to Dr. Fritsch for construction of probes. (Tr. 15, 128-30).

The second shipment of Miyake material arrived on May 30, 1984. (Tr. 15, 146). Dr. Miyake and his colleague, Dr. Shimizu, sent a note stating that this was a problematic sample and unreliable. (Tr. 15, 146-148). Dr. Hewick confirmed this

and did not rely on shipment two in formulating his conclusions. (Tr. 15, 155).

The third shipment from Dr. Miyake arrived on July 22, 1984. (Tr. 15, 156). Hewick received two samples in shipment number 3, which were designated as fractions two and three. Fraction two had an *in vitro* special activity of 83,005 IU/AU, and fraction three had a specific activity of 11, 266 IU/AU. (Tr. 15, 157). Hewick ran differing amounts of fraction two materials on RP-HPLC seven times, and determined that chromatographs were essentially the same as those from shipment one. (Tr. 15, 162-163). He took the material under the large peak, subjected it to tryptic digestion and sequencing, and determined that the material corresponding to the large peak was EPO. (Tr. 15, 169-71). *See* Figure B for a chromatograph of the EPO received from Dr, Miyake as printed in the '195 patent. (PX 500, Fig. 1).

Dr. Hewick calculated the specific activity of pure EPO by determining that "at least fifty per cent" of the area under the A280 trace of the chromatograph of fraction 2 of shipment three, was attributable to something other than EPO. (Tr. 15, 175-76). He did this by photocopying the chromatograph and then cutting out the area above the base line. (Tr. 15, 175). He weighed this piece of paper and then cut out and weighed the EPO peak. (Tr. 15, 175). He then calculated the ratio of the entire 280 area to the EPO area and multiplied this figure by the specific activity reported for this shipment, which was approximately 83,000 IU/AU. (Tr. 15, 175). Through this procedure, Dr. Hewick determined that the EPO area was less than fifty percent and that the specific activity should be twice the 83,000 IU/AU figure reported in the Miyake article or "at least about 160,000 IU/AU." (Tr. 15, 176-177).

As Amgen's own scientist conceded, the procedure of cutting and weighing chromatographs is a well-recognized technique used by protein chemists to examine this type of data. (Tr. 15, 175-76; 14, 153-154).

When Dr. Hewick performed work on shipment three, GI did not have the capacity to derive quantitative information from *in vivo* or *in vitro* bioassays. (Tr. 15, 171). Dr. Hewick received a fourth shipment from Dr. Miyake in October or November, 1984. He injected this shipment onto the reverse phase column and the resulting chromatograph had the same characteristic contaminants as shipments one and three. (Tr. 15, 194-196).

c. Use of RP-HPLC by other scientists on uEPO.

In October, 1985, Dr. Kawakita, a scientist at Kummamoto University in Japan, used a purification procedure which did not follow the Miyake procedure and which applied RP-HPLC to urinary EPO at two different steps (although not the final one), and found a specific activity level of 188,000 IU/AU. Chugai measured the material and found *in vivo* a specific activity of 180,000 IU/AU. (PX 721; Tr. 25, 24).

Charles Kung performed certain experiments in 1987 which confirmed the conclusions reached by Dr. Hewick. Kung has been using chromatographic purification techniques for purifying proteins in Dr. Goldwasser's laboratory at the University of Chicago since 1960. (Kung Dep. Tr. 11). Kung is one of the co-authors of the Miyake article. (PX 528). In the mid-1970's, the specific activity of uEPO processed in Dr. Goldwasser's laboratory ranged between 70,000 and 120,000 IU/AU. (Kung Dep. Tr. 16). He believed in 1976 that this EPO was homogeneous. (Kung Dep. Tr. 17).

In December, 1987, Kung subjected Fraction III of the uEPO, purified by Miyake on August 6, 1976, to RP-HPLC. (Kung Dep. Tr. 44). The original Miyake EPO had a specific activity of 53,973 IU/AU by *in vivo* assay. (Kung Dep. Tr. 44, 45). After the RP-HPLC, the Miyake EPO had a specific activity of 173,640 IU/AU. (Kung Dep. Tr. 44). The RP-HPLC removed contaminants from the original input material. (Kung Dep. Tr. 48). On July 21, 1987, Kung subjected another Miyake

EPO sample, which had been purified on July 27, 1976, to RP-HPLC. (Kung Dep. Tr. 51-52). The specific activity of the reverse phase EPO was 2.6 times that of the original EPO. (Kung Dep. Tr. 66). On August 29, 1988, Kung subjected Fraction IIIB from the 1976 Miyake EPO materials to RP-HPLC, and found that its specific activity was 134,130 IU/AU. (Kung Dep. Tr. 79-80). Table IV of the *Miyake et al.* article reported Fraction IIIB as having a specific activity of 71,250 IU/AU. (PX 528). At least by December, 1987, RP-HPLC became a standard final purification step used in the Goldwasser laboratory for the purification of urinary source EPO. (Kung Dep. Tr. 111-112).

d. Recombinant EPO purification efforts.

Jasbir Singh Seehra joined GI in May, 1983. (Tr. 20, 143). Originally listed as a co-inventor on the '195 patent, Seehra was responsible for the portion of the patent relating to the purification of recombinant EPO. (Tr. 20, 144-45). He did no work on the purification of EPO from natural sources. (Tr. 20, 151).

Seehra had also worked on the purification of recombinant Interleukin 2, which was produced in E. Coli cells and not glycosylated. (Tr. 20, 150-151). Seehra had to activate the protein before putting it on reverse phase. (Tr. 20, 157). The RP-HPLC did not inactivate the Interleukin 2. (Tr. 20, 157). His work on purifying recombinant tissue plasminogen activator ("TPA"), a glycosylated protein made in mammalian host cells, was successful; however, he was not successful in maintaining the activity of tissue plasminogen activator after the use of RP-HPLC. (Tr. 20, 152). In response to the question why the reverse phase deactivated TPA and not Interleukin 2, Seehra testified:

> And that's the mystery of purification when you use reverse phase, is that it may seem obvious to use it to

> get purification, but you don't know what the result is going to be. You put it on and you basically take a gamble. Sometimes you get activity, sometimes you don't. Sometimes the protein comes off and sometimes it doesn't.
>
> In the instances that it does come off, you know, it's a very powerful technique. It gives you a lot of purification. But sometimes you lose your protein on it.

(Tr. 20, 157).

On or about October 9, 1984, Seehra started work in trying to purify rEPO as part of his effort to develop large scale commercial purification procedures. (Tr. 20, 166, 197; PX 700). On or about November 19, 1984, Seehra provided a description of the procedures he used in the purification of EPO from COS-conditioned media to the patent attorneys. (PX 710, 711). The final purification step was RP-HPLC. (Tr. 20, 165). Seehra reported that the "pooled fractions of EPO contained 15.5 ug of EPO in 25 ug of total protein." (PX 711).

In Example 2 of the '195 patent, Seehara used the following purification steps: acid precipitation; carbonylmethyl sepharose chromatography, which separates EPO from other proteins based on charge; RP-HPLC on the mixture that was 2.5% EPO; and another run of RP-HPLC on the resulting mixture which was 33% EPO. (Tr. 20, 187-191). He did not use the Miyake procedure to purify the rEPO. (Tr. 20, 198).

Seehra explained that the reason the RP-HPLC was unsuccessful in purifying the rEPO was that "very impure material" was going on to the reverse phase. (Tr. 20, 200). If he had started off with "either high levels of expression or additional steps which resulted in more pure material before going on to reverse phase," he expected he would have been successful because Dr. Hewick had shown that RP-HPLC was successful

in purifying uEPO. (Tr. 20, 200-201). Hewick himself testified that a good expression of rEPO might make it easier to purify rEPO than uEPO. (Tr. 13, 45-46). Seehra had never compared the responsiveness of recombinant and natural EPO to RP-HPLC, but he reached this expectation based upon his reading of the literature that recombinant and natural source proteins behave the same on chromatographic columns. (Tr. 20, 201). However, the literature did not compare the behavior of recombinant and natural source proteins on RP-HPLC. (Tr. 20, 201-202).

The purification procedure used by Dr. Seehra, and reported in the '195 patent, did not result in purified rEPO, but rather the resulting solution after two runs of RP-HPLC had only 62 per cent EPO. (Tr. 20, 191-192).

The patent does not contain any procedures for increasing the expression in COS cells or for purifying rEPO to the point that RP-HPLC will be successful. (Tr. 20, 202-203). The only initial purification steps mentioned are the purification procedures used by Dr. Miyake and Dr. Goldwasser for urinary EPO. (Tr. 20, 203).

On November 25, 1985, GI shipped rEPO expressed from CHO cells which rose as a single peak on a chromatogram and was about 90% pure. (Tr. 13, 42-44; PX 760). The purification steps used to purify this recombinant EPO were different from the *Miyake et al.* paper, and did not use RP-HPLC as a purification step. (Tr. 13, 41-45).

By July and August, 1986, GI had concluded, based on bioassays, that the *in vivo* and *in vitro* specific activities of recombinant EPO were virtually the same, approximately 169,000 IU/AU. (Tr. 24, 175-76). In 1984 and 1985, Dr. Fritsch did not know what the specific activity of rEPO was but believed it would be the same as naturally-occurring urinary EPO. (Tr. 25, 13-14). He believed that the basic machinery for transcribing that DNA information into the protein should be the same in

both the mammalian cell, the recombinant CHO cell, and in the naturally-occurring cell; and that based on his past experience, the structure of the recombinantly expressed protein was the same as the structure of the naturally-occurring protein both at the protein level and at the glycoprotein level. (Tr. 25, 14).

Amgen itself specifies that the specific activity of EPO made by its recombinant technology is at least 160,000 IU/AU as determined by an *in vivo* bioassay. (PX 214; PX 525, Ex. C, p. 3).

e. Amgen's purification of rEPO.

In August 1984, Dr. Thomas W,. Strickland, an Amgen scientist, began work on the purification of human rEpo ("rHuEPO"). (Tr. 14, 72). He did not use RP-HPLC until another scientist named Por Lai suggested it on October 25, 1984. (Tr. 14, 75). He had used RP-HPLC about a month earlier as one of the steps to purify monkey rEPO, which is glycosylated. (Tr. 14, 76). By September 28, 1984, Amgen had also used RP-HPLC for the purification of non-glycosylated rHuEPO produced by E. Coli cells; the product was 95% pure. (PX2, Col. 33, 1. 137). In his November 30, 1984 patent application, Dr. Lin suggested the use of HPLC to recover mammalian cell expression products "in substantially purified form." (PX 3, p. 64).

From October, 1984 through March, 1985, Dr. Strickland experimented with purification processes that involved reverse-phase hydrophobic chromatography. (Tr. 14, 86). RP-HPLC is a subset of hydrophobic chromatography and differs only in the size of the particles in the column and the amount of pressure needed to push the liquid through. (Tr. 14, 88-89). On March 7, 1985, after analyzing certain gels on RP-HPLC materials for the purpose of discussions with the FDA, Strickland suggested a purificiation process which included RP-HPLC.

(Tr. 14, 83). The final purification process which Amgen selected for rEPO included reverse-phase hydrophobic chromatography as a step. (Tr. 14, 90).

VIII. DISCUSSION

a. '008 PATENT

A. Validity

Defendants have raised various arguments challenging the validity of the '008 patent. Pursuant to 34 U.S.C. § 282, patents are presumed valid, and the one attacking validity has the burden or proving invalidity by clear and convincing evidence. *Hybritech Inc.* v. *Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1375 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). This heavy burden of proof is deeply rooted in the nature of the judicial process, for it reflects the deference owed to the considered judgment of an expert, such as a patent examiner, skilled in areas of complex and specialized technology. *Spaulding & EvenFlo Companies, Inc.* v. *Acushnet Co.*, 718 F. Supp. 1023, 1031 (D. Mass. 1989). The burden is made more difficult when the prior art relied upon at trial is the same as that which was before the PTO. Although the introduction of prior art not before the examiner may facilitate the challenger's meeting the burden of proof on invalidity, the presumption remains intact and the clear and convincing standard does not change. *Hybritech Inc.* v. *Monoclonal Antibodies, Inc.*, 802 F.2d at 1375. The court will address each of defendants' arguments challenging the patent's validity separately below.

1. Anticipation Defense

Defendants argue that the '008 patent is invalid as fully anticipated by Dr. Fritsch's EPO work at GI. Before the court can address this argument, it must first determine what the "in-

vention" is. According to Amgen, the claimed invention is the DNA sequence encoding human EPO. (Amgen's Post-Trial Brief, tab 1, p. 16). In contrast, defendants argue that the claimed invention is a "purified and isolated" DNA sequence encoding EPO, or in other words, the cloned EPO gene, not the listing of 4000 bases. (Defendants' Joint Post-Trial Reply Brief, p. 7 n. 7).

The invention claimed in the '008 patent is *not* as plaintiff argues the DNA sequence encoding human EPO since that is a nonpatentable natural phenomenon "free to all men and reserved exclusively to none." *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980). Neither is it the approach called "the invention" by defendants in DX 827. Rather, the invention as claimed in claim 2 of the patent is the "purified and isolated" DNA sequence encoding erythropoietin. (*See* PX 2).

Defendants argue that Dr. Fritsch was the first to conceive this invention because he was the first person to formulate the probing strategy of using two sets of fully degenerate probes from two different regions to screen a genomic library, which was the strategy that eventually resulted in the successful cloning of the EPO gene. (DX 827). Defendants further argue that Dr. Fritsch exercised reasonable diligence in reducing the invention to practice, and that the '008 patent therefore is invalid under 35 U.S.C. § 102(g).

35 U.S.C. § 102 provides in relevant part:

> A person shall be entitled to a patent unless —
>
> ****
>
> (g) before the applicant's invention thereof the invention was made . . . by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable

> diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Under this provision, the one who first conceives the invention and exercises reasonable diligence in reducing it to practice will be awarded priority, even if another inventor reduced to practice first. *See* 3 D. Chisum, *Patents* § 10.03[1], at 10-20 (1989) (and cases cited therein).

a. Was the conception complete and operable?

Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Hybritech Inc.* v. *Monoclonal Antibodies, Inc.*, 802 F.2d at 1376, quoting 1 *Robinson on Patents* § 532 (1890). The idea must be of specific means, not just a desirable end or result, and must be sufficiently complete so as to enable anyone of ordinary skill in the art to reduce the concept to practice. 3 D. Chisum, *Patents* § 10.03, at 10-45 (1989).

In certain "unusual cases," an inventor may be unable to establish a complete conception of a given subject matter prior to reduction to practice, and "the work of conception must be considered to proceed simultaneously with the work of reduction to practice." *Alpert* v. *Slatin*, 305 F.2d 891, 894 (C.C.P.A. 1962); *see also* 3 D. Chisum, *Patents* § 10.04[5] (1989). This doctrine was enunciated by Robinson in his 1890 treatise as follows:

> In many inventions the act of conception is clearly distinct, in point of time, from that of reduction. . . . In many others the work of conception and reduction goes forward almost simultaneously, so nearly so that no date can be fixed as that before which the conception was complete and after which

> the reduction to practice was begun. *This is true in nearly all inventions which are the result of experiment, — where the inventor, instead of evolving the entire art or instrument out of his own thought, conjectures that such an act or substance will subserve a given purpose, and having tried it, finds that it accomplishes the end.* . . . Until that instant it is mere speculation, at most a probably deduction from facts already known; and the same act which reduces it to practice gives to the conception its definite and final form.

1 *Robinson on Patents* § 381 (1890) (emphasis added).

The court in *Alpert* v. *Slatin, supra*, stated that the doctrine is "rarely applied" to "a residuum of cases where results at each step do not follow as anticipated, but are achieved empirically by what amounts to trial and error. In this type of research, the investor's mind cannot formulate a completed invention until he finally performs a successful experiment." 305 F.2d at 894.

The question is one of fact as to completeness of the conception. *Standard Oil Co.* v. *Montedison*, 494 F. Supp. 370, 407 (D. Del. 1980), *aff'd*, 664 F.2d 356 (3d Cir. 1981), *cert. denied*, 456 U.S. 915 (1982). The mental formulation of the invention will be deemed "complete" if the inventor has conceived the means of putting that formulation in the hands of the public where no more than routine skill would be required to do so. *Rey-Bellet* v. *Engelhardt*, 493 F.2d 1380, 1387 (C.C.P.A. 1974).

Defendants characterize the "core dispute" with respect to their Section 102(g) defense as whether Dr. Fritsch's conception was a "generalized approach" which would result in "repeated failure and extensive experimentation" or whether it was an approach which by the exercise of ordinary skill ended in the isolation of the EPO gene. (Docket 391, p. 11).

Defendants have not demonstrated by clear and convincing evidence that in 1981 when Dr. Fritsch conceived his approach, which they characterize as "the invention," the approach would have enabled a scientist of ordinary skill to isolate the EPO gene. Dr. Leroy Hood testified that although he started talking in 1979 and 1980 about using microsequence analysis to make probes to clone genes, "[t]here are many technological difficulties that lie between being able to synthesize probes and clone a gene." (Hood Dep. Tr. 29). In 1981, the path-breaking concept of using oligonucleotide probes to hybridize with DNA sequences had just been published. (DX 200). No genomic library has been screened, and techniques for screening the less complicated cDNA library were in their infancy. Dr. Flavell testified that in 1981 there was "so little known about the power of the oligonucleotide screening methods." (Tr. 28, 18). Technical improvements, particularly in the use of filters, were required to handle complex probe mixtures, and scientists did not know whether a large number of radioactive probes would create too high a background noise to read a positive signal. (Tr. 27, 114; 28, 54). Because the experiments were "too crude" in 1981, Dr. Flavell believed that a scientist could not have screened half a million plaques. (Tr. 28, 72).

The structure of the EPO protein — for example, where the introns are located — was also unknown. Although Amgen concedes it was known in the art in 1980-1981 to prepare tryptic fragments from a protein and to then purify those fragments by high performance liquid chromatography to sequence the protein (AF 87), the art of sequencing was far from perfect in 1981. Dr. Hewick, an experienced protein sequencer and one of the inventors of the gas phase sequenator, was unable to obtain the correct n-terminal sequence for EPO at Cal Tech in the fall of 1980; he was unsure of the amino acids at positions 3 and 7, and was incorrect about the amino acid at position 24. Even in 1983, Biogen's attempt to sequence EPO resulted

in the same error at position 24. As Dr. Davies and even Dr. Sadler, Chugai's expert, testified, success could not be predicted until the gene was in fact isolated. (Tr. 8, 37; Sadler Dep. Tr. 95).

Given the utter lack of experience in probing genomic libraries was fully degenerate probes and the crudeness of the techniques available in 1981, it would have been mere speculation or at most a probable deduction from facts then known by Dr. Fritsch that his generalized approach would result in cloning the EPO gene. If any fact situation triggers the simultaneous conception and reduction to practice doctrine, this is it. It was not until Dr. Fritsch actually had the sequence information in hand that he could give his conception its definite and final form. For example, Dr. Fritsch could not have possibly determined whether probing with two fully degenerate sets of probes from different regions was even feasible until he saw the precise amino acid sequence of the gene. If the sequences had been too degenerate, guess mers might have been necessary or subsets preferable, just as happened with the cloning of the Factor VIII gene. As Dr. Sadler testified, the approach to be tried depends on the kind of amino acid sequence. (Sadler Dep. Tr. 87-88).

The most compelling argument raised by defendants against the use of the doctrine is that both Dr. Fritsch and Dr. Lin succeeded in cloning the gene in 1983 using this approach as soon as they obtained accurate sequence information. However, with respect to 1981, the year defendants urge as the priority date, defendants have produced no evidence that screening a genomic library with a large number of mixed probes was not characterized by perplexing and intricate difficulties arising every step of the way.

It is true that Amgen held an advantage over the other companies because it alone among the commercial biotechnical companies had access in usable amounts after 1981 to urinary

source EPO, which was a "rather rare commodity," from Dr. Goldwasser, the primary person who had that material. But, that fact, although making for an unequal playing field with respect to the opportunity to reduce the invention to practice, does not undermine this court's determination that the doctrine of simultaneous conception and reduction to practice is applicable.

Moreover, even if the doctrine were inapplicable, the approach of using two sets of fully degenerate probes from two different regions to screen a genomic library was not complete and operable in 1981. GI has not provided clear and convincing evidence that this information was sufficient to enable one with ordinary skill in the art to reduce the invention to practice in 1981 or even 1982. By 1982, Dr. Flavell said it would be obvious to try to probe a genomic library but he would be "anxious about the outcome of it." (Tr. 28, 75-76). No evidence was presented that in 1982 a genomic library had been screened successfully. Although defendants argue that constructing probes and screening DNA libraries were "all well-known techniques in the art," they point only to evidence indicating that these methodologies were available to a person with ordinary skill in the art *in 1983*. (DF III-33, 34, 35). This evidence is insufficient to amount to clear and convincing evidence that Dr. Fritsch's conception was complete and operable *in 1981*.[3]

Defendants argue that any claim that Dr. Fritsch's cloning stragety was incomplete is contradicted by Dr. Lin's status as the sole inventor named on the '008 patent. They state that Dr. Lin's contribution to Amgen's EPO project was devising the successful cloning strategy, and argue that if other inventive work was necessary to reduce the invention to practice — that

[3] Although the question would be much closer if the relevant year were 1983, the court has found that even though it would have been obvious to one of ordinary skill in the art *to try* this screening approach in 1983, there would have been no reasonable expectation of success in 1983. (*See* p. [A116] *infra*).

is, work beyond that which could be done by one with ordinary skill in the art — there is no explanation for Amgen's failure to name the responsible scientists as joint inventors on the '008 patent. However, this argument is a red herring because even assuming in 1983, when Dr. Lin filed his patent application, these other cloning skills were routine, the focus for determining whether Dr. Fritsch's conception was complete and operable is 1981. Moreover, the naming of Dr. Lin as the sole inventor on the patent does not mean that the invention was based solely on the formulation of the successful cloning strategy, but rather the combination of that novel technique with other techniques which by 1983 "were available to those of ordinary skill in the art."[4]

In the alternative, defendants argue that even if the descriptions given by Dr. Fritsch to Dr. Maniatis in 1981 were too general, "there can be no similar argument with respect to Dr. Fritsch's use of the invention in October, 1982, almost a year prior to Dr. Lin." (Docket 388, p. 7). It is true that Dr. Fritsch used two sets of fully degenerate probes to screen a genomic library in October, 1982, before Dr. Lin. Moreover, GI has pointed to evidence that "prior to 1983" certain cloning techniques, like synthesizing oligonucleotide probes, were available to those of ordinary skill in the art. (DF III-34). However, even though there is evidence that the screening techniques were improving, defendants have not demonstrated by clear and convincing evidence that even in October, 1982 the conception would have enabled one of ordinary skill in the art to reduce the invention to practice by screening a genomic library.[5]

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[4] In any event, Dr. Lin was the head of the EPO project at Amgen through 1984 with supervisory power over all aspects of the invention.

[5] Defendants point out that the PTO declared an interference in a letter dated May 9, 1989 forwarding the case to the Board of Patent Appeals and Interferences. (DX 441). However, this declaration is merely a determination that a *prima facie* case has been presented based on an *ex parte* showing by the applicant. (*See* Tr. 35, 14-15).

b. Priority of conception.

In any event, even assuming that the doctrine of simultaneous conception and reduction to practice does *not* apply here, and that the conception was sufficiently complete and operable in 1981, the court would still reach the same conclusion that Dr. Lin has priority over Dr. Fritsch as the inventor of the "purified and isolated" DNA sequence encoding erythropoietin because Dr. Lin conceived the approach first of using two sets of fully degenerate probes from two different regions to screen a genomic library.

As a general rule, the date an application adequately disclosing the invention is filed is presumed to be the date of invention. 3 D. Chisum, *Patents* § 10.03[1], at 10-25 (1989). The inventor bears the burden of proving an earlier date of invention by showing either an earlier actual reduction to practice or an earlier conception and diligence to reduction to practice. *Id.* Conception must be proved *by corroborating evidence* which shows that the inventor disclosed to others his "completed thought expressed in such clear terms as to enable those skilled in the art" to make the invention. *Coleman* v. *Dines*, 754 F.2d 353, 359 (Fed. Cir. 1985), quoting *Field* v. *Knowles*, 183 F.2d 593, 601 (C.C.P.A. 1950). It is well-settled that the uncorroborated and undocumented testimony of the patentee is insufficient to prove invention date. *Kardulas* v. *Florida Machine Products Co.*, 438 F.2d 1118, 1121 (5th Cir. 1971).

Here, Dr. Lin testified that he discussed the screening of cDNA and genomic libraries with two sets of oligonucleotide probes to isolate the EPO gene with Dr. Marty Cline prior to October 27, 1981. (Tr. 4, 32-33). Dr. Fritsch testified that he came up with his cloning strategy a little later in November or December, 1981 and told Dr. Maniatis about it before Christmas, 1981. (Tr. 25, 126, 134-35). Dr. Lin's testimony is corroborated by the notes of Dr. Cline taken on October 27, 1981, which Dr. Cline identified as his handwriting in his depo-

sition before the ITC.[6] These notes stated in relevant part that Phase 2 in January-March, 1982 would involve the screening of cDNA libraries with two sets of probes, and if such screening were negative, the screening of genomic libraries. (PX 170A, 170B). Dr. Lin testified that these notes refreshed his recollection about his conversations with Dr. Cline, and reflected the content of those conversations, and the court found his testimony credible.

Defendants argue that there is no evidence other than Dr. Lin's testimony that Dr. Cline's notes were based on conversations with Dr. Lin. Moreover, Dr. Cline testified in general at his deposition that he could not remember which suggestions for the EPO project he generated and which suggestions were proposed by Amgen people. (Cline Dep. Tr. 12). However, Dr. Lin was the head of Amgen's EPO project at that time, and in fact he and his assistant were the only two working on the EPO project at Amgen. (Tr. 5, 33). Maureen Gilmore-Hebert, who had been working on the EPO project before Lin joined Amgen in August, 1981, did not work on the EPO project after his arrival there. (Tr. 5, 79). Therefore, the court finds

[6] The court denied GI's *in limine* motion to exclude the deposition of Dr. Cline, a witness residing in California, taken under oath during the course of the ITC proceedings pursuant to Fed. R. Evid. 801(b)(1) and Fed. R. Civ. P. 32(a)(3). First, Chugai, the defendant in the ITC proceedings, is GI's exclusive licensee, and has an identity of interest with respect to the validity of the '008 patent. It had the opportunity and identical motive to examine Cline, who was Amgen's consultant on EPO. Moreover, the instant law suit was pending so that both Chugai and GI were on notice of the significance of Cline's testimony. Second, although the ITC was operating under a different statutory standard, the administrative law judge focused on many of the same issues with respect to the validity of the '008 patent as were examined in this proceeding. (PX 43, pp. 133 *et seq.*). Third, in order to expedite discovery and to obviate the need to duplicate document production and retake depositions, the court ordered the parties to share the discovery taken during the course of the ITC proceedings. GI never notified the court of any objection to using depositions taken during the course of that proceeding in this trial. Finally, in light of the significance of the Cline deposition and the possible prejudice to GI, the court gave GI the opportunity to take Dr. Cline's deposition in California during the course of the trial. GI never sought to introduce any supplemental deposition transcripts of Dr. Cline.

from this evidence that it is more probable than not that the notes arose from conversations with Lin.

Defendants also argue that neither the notes nor Dr. Cline's testimony describe in full the successful cloning strategy used by Dr. Lin in 1983. They point out that there is no evidence that Dr. Lin ever designed or used two sets of fully degenerate probes from two different regions to screen a genomic library prior to September, 1983, whereas Fritsch used this methodology early on, beginning in September, 1982. However, the reference in Cline's notes to two sets of probes could only have referred to sets of probes from two different regions of the amino acid sequence. Dr. Lin's notes in April, 1982, concerning an EPO project team meeting mentioned the need for confirming genomic clones with a probe from a second region of the amino acid sequence after describing the alternative routes to looking for the EPO gene pointed out by Dr. Cline. Moreover, as early as March, 1982, Lin had designed two sets of probes from different regions of the amino acid sequence, one of which was fully degenerate. (*See* PX 170C; Tr. 5, 107-108).

The question whether the corroborating evidence shows that Lin conceived of using *fully degenerate* sets of probes as early as October, 1981 is more troublesome. Although Dr. Lin testified that he meant sets of probes which could be fully or partially degenerate in his discussions with Dr. Cline, Dr. Cline's notes are non-corroborative as they do not mention the degeneracy of the probes at all. However, Dr. Lin did order a fully degenerate set of probes in early 1982,[7] and did use a fully degenerate probe as early as May 1982, which indicates that he did have in mind the use of fully degenerate as well as

[7] The evidence is unclear whether Dr. Lin ordered these probes as early as January, 1982 or in March, 1982. (*See* p. [A64] *supra*).

partially degenerate probes. Defendants emphasize the fact that Dr. Lin did not actually use two sets of fully degenerate probes to screen a genomic library until 1983. Dr. Lin has testified that his strategy was to try first the easier approach of designing partially degenerate probes with the highest probability of success before going to the fully degenerate probes where the prognosis was less clear. (Tr. 4, 56; 5, 61). This strategy makes sense in light of Dr. Flavell's testimony concerning the primitive nature of the screening techniques in 1981 and even 1982. In any event, even though Lin had definitely not decided by October, 1981 that fully degenerate probes were the only kinds of probes to use or even the best kind, neither had Fritsch. Dr. Fritsch himself decided to use partially degenerate probes from the highly degenerate region between residues 14 and 19, after failing to isolate the EPO gene using fully degenerate probes from the amino acid region 18-26. Moreover, on August 12, 1982, in describing his cloning Approach I, Dr. Fritsch stated that several probes "of limited degeneracy could be prepared" from available amino acid information. (PX 37A).

Accordingly, the court concludes that 35 U.S.C. § 102(g) does not apply here as plaintiff has shown by corroborating evidence that Dr. Lin conceived of the probing methodology before Dr. Fritsch.

c. Diligence in Reduction to Practice.

In addition, the court further finds that even if Dr. Fritsch were the first to conceive the invention, defendants have not shown he was reasonably diligent in reducing it to practice. The reasonable diligence standard balances the interest in rewarding the encouraging invention with the public's interest in the earliest possible disclosure of invention. *Griffith* v. *Kanamaru*, 816 F.2d 624, 626 (Fed. Cir. 1987). The case law reveals a "common thread" that courts may consider the reasonable everyday problems and limitations encountered by an in-

ventor as excuses for inactivity in reduction to practice. *Id.* However, by the same token, "[o]ne having the first complete conception of an invention cannot hold the field against all comers by diligent efforts, merely, to organize and procure sufficient capital to engage in the manufacture of his device or mechanism for commercial purposes." *Id.* at 628 (holding that Cornell University's decision against funding the inventor's project, which caused a delay in reducing the invention to practice while Cornell solicited outside funding, was not an excuse for inactivity in reduction to practice and constituted an assumption of "the risk that priority in the invention might be lost to an outside inventor").

Here, the evidence is undisputed that Dr. Fritsch decided in August or September, 1982 to focus his efforts on cloning the EPO gene using currently available n-terminal sequence information from Dr. Hewick. (Tr. 26, 11-12, 15-16). Dr. Fritsch had abandoned the approach of obtaining additional erythropoietin for further sequence information in August or September, 1982 because the terms that Dr. Miyake was asking for in exchange for supplying EPO to GI were "well beyond what GI at the time could afford." (Tr. 26, 18). Gabriel Schmergel, president and chief executive officer of GI, testified that 10-20% of GI's total resources would have been required to satisfy Miyake's demands. (Tr. 29, 83). No other attempts were made to obtain EPO from Miyake until early 1984, *after* Dr. Lin had successfully cloned the EPO gene, and there is no evidence in the record that GI even attempted within the intervening period to obtain outside funding to purchase the additional EPO from Miyake.[8] Dr. Miyake testified in a deposition that he did not have the facilities or staffing to purify EPO in

[8] Dr. Fritsch did testify that GI was contacting companies, such as Sandoz and Toyobo, "with the hope that they might be able to support us." (Tr. 26, 18). However, no testimony was offered as to whether these contacts continued after GI decided to abandon the approach of obtaining additional EPO in 1982.

September, 1982 and that he spent the following year on other research. (Miyake Dep. Tr. 212-213).

By April or May, 1983, after four failed attempts to clone the EPO gene from available sequence information, Dr. Fritsch had concluded that there was a problem with the available sequence information. (Tr. 26, 56-57). On June 1, 1983, GI contacted Dr. Sytkowski to obtain additional urinary EPO or sequence information without success. On July 12, 1983, GI contacted Dr. Judith Sherwood because she had a cell line from a kidney carcinoma cell making EPO. (Tr. 26, 61). The test results on the biological activity were ambiguous. (Tr. 26, 62). In one case, there was little evidence of EPO activity, and in the other, there was good evidence of activity. (Tr. 26, 62). GI entered into a collaboration with Dr. Sherwood in October, 1983, but in November or December, 1983 decided there wasn't enough EOP produced by the cell line to make it worth purifying. (Tr. 26, 63-64). Dr. Sherwood also gave GI some partially purified uEPO but there was not enough for sequencing. (Tr. 26, 65-66). There is no evidence that GI during this time period tried to resume negotiations with Dr. Miyake or tried to get funding for the materials.

The lack of evidence of any efforts to obtain funding to afford EPO from Dr. Miyake undermines GI's claim of reasonable diligence. Attempts to get EPO from Sytkowski and Sherwood, without more, do not demonstrate reasonable diligence in obtaining additional sequence information because Dr. Fritsch had no reasonable assurances that either scientist had sufficient amounts of pure EPO for sequencing. Indeed, in light of the fact that results of biological activity tests on Dr. Sherwood's cell line were so ambiguous, it was not reasonable to pursue only that source for pure EPO through the end of 1983.

Because Dr. Fritsch knew by May, 1983 that it was imperative to get new sequence information, and because one of the primary sources for usable amounts of urinary EPO for sequencing was Dr. Miyake, the only reasonably diligent approach at

that point was to recontact Miyake and seek out funding to obtain that information. GI has not given any explanation as to why it waited eight months to contact Miyake again, and has not submitted any evidence about its ability to afford Miyake's terms after May, 1983. By making the financial decision to pursue the alternative routes with Dr. Sytkowski and Dr. Sherwood without seeking outside funding or reinstating negotiations with Miyake earlier, GI assumed the risk that priority in the invention might be lost to another inventor in the interim.[9]

2. Obviousness

Defendants argue that the '008 patent is invalid as obvious under 35 U.S.C. § 103 because in 1983, when Dr. Lin cloned the EPO gene, the probing strategies used by him had been disclosed in prior art references and were widely practiced in the biotechnology industry. Pursuant to 35 U.S.C. § 103, a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."

In the landmark case on obviousness, *Graham* v. *John Deere Co.*, 383 U.S. 1 (1966), the Supreme Court articulated the following test:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and

[9] In addition, it took nine months after Dr. Fritsch conceived the approach in December, 1981 to start the EPO project at GI. Although Dr. Fritsch had certain pre-existing teaching commitments, such as teaching at Cold Spring Harbor over the summer, which precluded him from starting earlier, this personal weighing of priorities is not an excuse for such a long period of inactivity in reduction to practice. Further, there is no explanation as to why GI could not hire a scientist of ordinary skill in the art to begin the project, under Dr. Fritsch's supervision, while he was teaching.

> the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Id. at 17-18.

The proper approach to the obviousness issue must start with the claimed invention as a whole. *Kimberly-Clark Corp.* v. *Johnson & Johnson*, 745 F.2d 1437, 1448 (Fed. Cir. 1984). The invention as a whole embraces the structure, its properties and the problem it solves. *In re Wright*, 848 F.2d 1216, 1219 (Fed. Cir. 1988). The determination of whether a novel structure is or is not "obvious" requires cognizance of the properties of that structure and the problem which it solves, viewed in light of the teachings of the prior art. *Id.*

An invention is not obvious merely because it is a combination of old elements each of which was well known in the art at the time the invention was made. *Kimberly-Clark Corp.* v. *Johnson & Johnson*, 745 F.2d at 1448; *Reiner* v. *I. Leon Co.*, 285 F.2d 501, 503 (2d Cir. 1960), *cert. denied* , 366 U.S. 929 (1961). Rather, if such a combination is novel, the issue is whether bringing them together as taught by the patentee was obvious in light of the prior art. *United States* v. *Adams* 383 U.S. 39, 50 (1966). The critical inquiry is whether "there is something in the prior art as a whole to *suggest* the desirability, and thus the obviousness, of making the combination." *Fromson* v. *Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1985) (emphasis in original), citing *Lindemann Maschinenfabrik GMBH* v. *American Hoist & Derrick Co.*, 730

F.2d 1452, 1462 (Fed. Cir. 1984). In other words, obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988), quoting *ACS Hospital Systems, Inc.* v. *Montefiore Hospital*, 732 F.2d 1572, 1577 (Fed. Cir. 1984).

Whether a particular combination might be "obvious to try" is *not* a legitimate test of patentability. *Id.* However, the meaning of this maxim is sometimes lost since "[a]ny invention that would in fact have been obvious under § 103 would also have been, in a sense, obvious to try." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). The admonition that "obvious to try" is not the standard under § 103 has been directed mainly to the following situations: (1) where what was "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful; and (2) where what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *Id.*

"A patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified." *In re Sponnoble*, 405 F.2d 578, 585 (C.C.P.A. 1969). "This is *part* of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103." *Id. See also Eibel Process Co.* v. *Minnesota & Ontario Paper Co.*, 261 U.S. 45, 68 (1923). Moreover, a patent may claim a previously unattainable product, even if the product was

known to be clearly desirable, if the methods for making the product were nonobvious. *Cf. In re Coker*, 463 F.2d 1344, 1348 (C.C.P.A. 1972) (holding that a prior art reference which showed the desirability of producing certain compounds as possible cancer chemotherapeutics, but which employed an unsuccessful process in making the compounds, did not anticipate the claimed invention).

The question is whether what the inventor did would have been obvious to one of ordinary skill in the art attempting to solve the problem upon which the inventor was working. *In re Wright*, 848 F.2d at 1219. Obviousness does not require absolute predictability of success; rather, all that is required for obviousness under § 103 is a "reasonable expectation of success." *In re O'Farrell*, 853 F.2d at 903-04.

Here, plaintiff claims that the '008 patent is distinguishable from the prior art because "nowhere in the prior art is found the genetic sequence coding for human EPO." (Amgen's Post-Trial Brief, tab 1, p. 31). Plaintiff also asserts that the vector and host cell claims differ from the prior art because "vectors and transformed host cells containing the human EPO gene also were unknown prior to Lin's invention." (*Id.*). Although this argument may have been relevant with respect to defendants' anticipation defense, which requires defendants to demonstrate "identity of invention," the standard is different for determining obviousness or nonobviousness under 35 U.S.C. § 103. The question in the obviousness context is whether what the inventor did would have been obvious to one of ordinary skill in the art attempting to solve the problem upon which the inventor was working. *See In re Wright*, 848 F.2d at 1219.

In order to make a determination whether the '008 claimed invention was obvious, a review of the prosecution history is helpful. During the prosecution of the '008 patent, the patent examiner initially rejected certain claims as "obvious" based on

prior art references which taught in combination cells from which erythropoietin RNA can be isolated, the making of cDNA from RNA, and the cloning of a desired strand of DNA. (DX 207, tab 8, p. 8). In response, Amgen filed an amendment and reply which provided in relevant part as follows:

> It is highly pertinent to the issue of whether the cited references render Applicant's invention obvious that his isolation of DNA encoding human erythropoietin did *not* proceed by cDNA techniques attributed to the references and that his isolation of monkey cDNA encoding erythropoietin employed DNA/DNA hybridization methods and materials nowhere described or suggested by the references. As conspicuously noted in the present specification, Applicant's isolation of human EPO-encoding DNA was by screening of a human *genomic* library of 1,500,000 viral plaques . . . The improved methodology employed by Applicant is itself the subject of non-elected claim 60 which describes use of multiple mixed probes, specific substrates, protease enzyme treatment, specific probe concentrations and specific hybridization conditions. The success achieved by Applicant through practice of these procedures must be viewed in the context of the essentially concurrent pronouncement of the Anderson, et al. reference . . . that such screening methods are ". . . impractical for isolation of mammalian protein genes when corresponding RNA's are unavailable."

(DX 207, tab 12, pp. 27-28) (emphasis in original).

After Amgen submitted this reply, the patent examiner again rejected claims under consideration as "obvious" based on different prior art references. (DX 207, tab 13, pp. 4-6). The patent examiner stated in part that it would be obvious to isolate

the human EPO cDNA sequence by utilizing the erythropoietin amino acid sequence data set forth in the Sue, et al. prior art reference in order to devise oligonucleotide probes for use in screening a cDNA liver library in the manner taught by other prior art references. (*Id.*, p. 5).

In a second amendment and reply, Amgen responded to the patent examiner's new obviousness concerns in relevant part as follows:

> Applicant succeeded in his discovery of DNA encoding erythropoietin using screening procedures which are themselves submitted to involve patentable advances in the art of DNA hybridization . . . . More specifically, Applicant employed two distinct sets of mixed probes to find the human genomic sequence. The first set consisted of a mixture of 128 20-mers . . . . The amino acid sequence which formed the basis for construction of the first set of probes is now known to correspond to residues 46-52 of human erythropoietin. Applicant used *both* the set of 128 20-mers . . . *and* a second set of 128 17-mers (. . . relating to the sequence now known to correspond to erythropoietin residues 86-91) to jointly probe 1,500,000 phage plaques of human genomic library for the human sequence . . . . Applicant's use of mixed probes for screening a DNA library (and especially a mammalian genomic library) where the message sought was present in low abundancy had been projected as being "impractical" shortly before applicant's successful work.

(DX 207, tab 15, pp. 16-17) (emphasis in original). Amgen also stated:

> To Applicant's knowledge, 128 mixed probes had never before been successfully employed in screen-

> ing a cDNA library, much less a human genomic library which is approximately one hundred times more complex than a cDNA library . . . .
>
> ****
>
> Because Applicant could not have used the Sue et el. (sic) reference information to follow the Breslow et al. and Woods et al. procedures to screen a human genomic library or a monkey cDNA library without substantially departing from the quite simple procedures disclosed in the references, it cannot properly be argued that the claimed subject matter would have been obvious to a person of ordinary skill in the art at the time Applicant's invention was made.

(*Id.*, pp. 24-25).

After this second reply by Amgen, the patent examiner rejected certain claims in a third office action as "obvious" based on the prior art work of Goldwasser et al., Weiss et al., and Egrie taken in view of other prior art references (DX 207, tab 17, p. 5). The patent examiner stated that based on these prior art references it would be obvious to prepare EPO as a fused peptide by extracting the mRNA for EPO from kidney cells known to be rich therein and converting that mRNA into a cDNA library, and also to use a prior art isolating technique together with monoclonal antibody to human EPO as taught by Goldwasser, Weiss and Egrie as a probe for isolating a clone producing EPO. (*Id.* pp. 5-6). The patent examiner concluded with the statement: "At best only routine genetic engineering techniques would be involved." (*Id.*, p. 6).

In response to this office action, Amgen filed a third amendment and reply which provided in relevant part:

> Applicant notes at the outset that the presently claimed subject matter involves novel *DNA*, *not* a novel method for obtaining it.

(DX 207, tab 20, p. 17) (emphasis in original). Amgen went on to distinguish the prior art references cited by the patent examiner, stating:

> At best, the Examiner can only state that the invention *might* have been achieved by means other than those employed by Applicant. Such speculation is not an appropriate basis for a conclusion of obviousness. Were Applicant claiming an invention in an antibody screening method for isolating erythropoietin-encoding DNA, the art relied on might be pertinent. Applicant here claims specific new products never before in the possession of the public. That he *might* have brought them into existence by some other, untested means alluded to by the prior art references is not pertinent to patentability.

(*Id.*, pp. 22-23).

There were no other objections made on obviousness grounds by the patent examiner.

The court concludes based on this review of the prosecution history that the unique probing and screening method employed by Dr. Lin in isolating the EPO gene was what distinguised the invention from the prior art. In distinguishing the prior art references which Amgen believed were relevant,[10] Amgen did rely on Dr. Lin's use of two sets of 128 mixed probes to jointly probe the human genomic library, which previously had been pronounced as an "impractical" method for isolating mammalian protein genes.[11]

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[10] Amgen contends that the level of ordinary skill in the art at the time of filing the application was a person with a PhD or perhaps an M.D. doing research at that time and having one or two years of post doctoral experience in DNA research. (AF 166). Defendants do not contest this assertion. (DF III-20).

[11] Amgen has not argued that obtaining sequence information for the EPO protein was inventive. Wall testified that if a person skilled in the art in Septem-

Defendants have shown by clear and convincing evidence that the probing and screening procedures used by Dr. Lin were "obvious to try." Dr. Flavell, defendants' expert witness, who currently is the chairman and professor of immunobiology at Yale University and who was the president in charge of research at Biogen in Cambridge, Massachusetts from 1982 through the summer of 1988, testified that based on the state of the art in September, 1983, it would have been obvious to a person of ordinary skill in the field of gene cloning to try to isolate the EPO gene using two sets of fully degenerate probes corresponding to different regions of the amino acid sequence to screen a genomic DNA library. (Tr. 28, 18).

Dr. Julian Davies, who is professor and head of the Microbial Engineering Unit at the Pasteur Institute in Paris, and who held the equivalent position to Dr. Flavell at Biogen's offices in Geneva, Switzerland from 1980 through 1985, also testified that it would have been "obvious to try" cloning the EPO gene if the EPO fragments that were available to Dr. Lin in 1983 had been made available to Biogen. (Tr. 8, 51). Dr. Lin himself testified that the use of two sets of probes or the use of fully degenerate probes was not particularly innovative. (Tr. 4, 52). Indeed, Dr. Fritsch tried this approach as early as October, 1982 in his attempt to isolate the EPO gene at GI. (Tr. 26, 21-23, 32-33).

However, although the question is a close one, defendants have not demonstrated by clear and convincing evidence that there was a "reasonable expectation of success" in cloning the EPO gene based on this probing strategy. With respect to this issue, there was a difference of opinion among the experts. In

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ber, 1983 were to receive fragments from the EPO protein, he would have been able to obtain amino acid sequences for those fragments. (Tr. 3, 128). Indeed, Amgen has conceded it was "known in the art in 1980-81 to prepare tryptic fragments from a protein and to then purify those fragments by high performance liquid chromatography (HPLC) to sequence the protein." (AF 87).

his testimony at trial, Dr. Davies stated that although "it would be obvious to try," he could not say whether Biogen scientists would have succeeded in cloning the EPO gene if Biogen had the erythropoietin fragments that were available to Dr. Lin in 1983. (Tr. 8, 51). He did state in the ITC proceeding that "[i]f we had a fantastic library and we had those same probes . . . mentioned in the Lin patent — I am sure we would have done it." (Tr. 8, 53). However, he qualified that statement by saying, "But, you know, I am putting a lot of things together." (*Id.*).

Dr. Wall, one of plaintiff's expert witnesses who is currently a professor in the Microbiology and Immunology Department at the UCLA School of Medicine and who has done extensive research primarily in the field of genetics, molecular biology and recombinant DNA technology since receiving his PhD in microbiology in 1970, also testified at trial that it would have been "difficult," no greater than a 50% chance, to find the EPO gene in September-October, 1983 by screening a genomic library with two sets of fully degenerate probes from two separate regions of the amino acid sequence. (Tr. 3, 146-48). He said, "you couldn't be certain where in the genomic DNA your probe might fall," and mentioned as an example that if the probe happened to be a sequence which spanned an intron-exon juncture, then it would not hypbridize. (Tr. 3, 148). In fact, that precise problem happened at Biogen since the major probe used there — a 20-mer of 128-fold redundancy based on the first nine residues of the amino acid sequence — was interrupted by an intron. (Tr. 27, 68-69, 78). Further, and most significantly, no one had successfully screened a genomic library using fully degenerate probes of such high redundancy as the probes used by Dr. Lin. There was, therefore, no way of knowing whether a high background of radioactivity would occur making it impossible to discern positive hybridizations.

On the other hand, Dr. Flavell did give an expert opinion that by 1983 there was a reasonable expectation of success in

isolating the EPO gene with the approach of using two fully degenerate sets of probes corresponding to different regions of the amino acid sequence to screen a genomic library. (Tr. 28, 18-19). However, his testimony does not rise to the level of clear and convincing evidence for a few reasons. First, Biogen, the company where he worked at the time, did not begin to use a genomic library in screening for the EPO gene until the end of 1983 or the beginning of 1984, *after* Dr. Lin had already succeeded in cloning the gene. Second, Dr. Flavell's testimony must be weighed against the testimony of plaintiff's experts, including Dr. Davies who was Flavell's counterpart at Biogen's offices in Switzerland.

Finally, and most significantly, Dr. Flavell based his opinion on prior art references which do not show, even in combination, that such an approach was likely to succeed. Only one of these prior art references — the Seki, et al. abstract — dealt with the screening of a genomic library using two sets of fully degenerate probes. However, the probes used were not highly degenerate, only of 48-fold and 16-fold redundancy, and there is no indication in the abstract that the experiment was actually successful in isolating the gene of interest. (DX 185).

The prior art references relied on by Dr. Flavell did show that two fully degenerate sets of probes could be used to isolate a cDNA clone (DX 204); that a single probe of extremely high degeneracy could successfully isolate a gene from a human cDNA library (DX 203); that two probes of single redundancy from separate regions could successfully be used to screen a genomic mouse DNA library (DX 183); and that two probes, one fully degenerate and one not, could successfully be used to screen a porcine genomic library (DX 7). But, none of these prior art references suggests that the probing strategy of using two fully redundant sets of probes, of relatively high degeneracy, to screen a human genomic library would be likely to succeed in pulling out the gene of interest. The prior art references

on the screening of cDNA libraries do not support the argument that there was the same expectation of success in screening a human genomic library, which is much larger and more complex. The prior art references on the screening of genomic libraries are distinguishable because they did not employ two fully degenerate sets of probes or sets of probes of as high a degeneracy as the probes used by Dr. Lin. Dr. Flavell himself testified that the prior art publications culminating in the '008 patent show a "gradual evolution," which added incrementally to the available information in the field of cloning. (Tr. 28, 23).

Defendants have cited other testimony to support their claim that there was a reasonable expectation of success. Specifically, they refer to the trial testimony of Dr. Axel Ullrich, one of plaintiff's expert witnesses with respect to the fields of molecular biology, recombinant DNA technology and gene cloning, who is presently director of the Department of Molecular Biology at the Max Planck-Institute fur Biochemie in West Germany and who worked at Genentech from 1979 to 1988 first as a senior scientist and then as a staff scientist. Dr. Ullrich testified that in 1983 there was a probability of success in using mixed oligonucleotide probes to screen a DNA library. (Tr. 7, 76). However, his testimony was during a line of questions concerning his efforts to screen a cDNA library. (Tr. 7, 75). He did not address whether the use of fully degenerate sets of probes, of relatively high redundancy, to screen a genomic library was reasonably likely to succeed. Moreover, he later testified that "the crucial aspect" of his opinion was that the approach was "unpredictable," and also stated that although the approach "appears to be straightforward on paper, . . . it is in reality not straightforward at all" and "a problem with any one of [the individual steps] can lead the experimenter into difficulty." (Tr. 7, 15, 70, 117).

Defendants also rely on the testimony of Dr. Jasper Sadler before the ITC. Dr. Sadler directs a biochemical molecular

biology research laboratory at Washington University and cloned the plasminogen gene. He was an expert witness on behalf of Chugai during the ITC proceeding. He testified that he would have expected that those skilled in the art could have and would have been successful in cloning the EPO gene using the approaches known and available in 1983 if the amino acid sequence information were available. (Sadler ITC Tr. 826-27, 848). He also stated that as of 1983, the methodology Dr. Lin used in the '008 patent was not a "novel contribution." (*Id.* at 851-52).

However, Dr. Sadler's own deposition testimony undercuts his ITC testimony. He testified: "In principle, a synthetic oligonucleotide probe should be adequate to identify the right sequence in a genomic library or cDNA library if it is present. In practice, many factors can conspire to make the project unsuccessful." (Sadler Dep. Tr. 86). For example, he pointed out that if a probe sequence is represented hundreds or thousands of times, the number of false positives would increase and there would be a problem of seeing the true positive among the potential false ones. (Sadler Dep. Tr. 87). He described the approach taken by Amgen as a "highly risky approach" which in 1982-1984 he would not have had confidence would work "in prospect." (Sadler Dep. Tr. 87, 95). Dr. Sadler said that given a certain kind of amino acid sequence, the approach to be tried is fairly predictable: "It is trial and error, but the game is fairly clear." (Sadler Dep. Tr. 87-88). This testimony does not amount to clear and convincing evidence that the approach used by Dr. Lin in cloning the EPO gene could reasonably be expected to succeed in 1983.

Accordingly, the court concludes that defendants have not shown by clear and convincing evidence that the probing and screening procedures used by Dr. Lin to isolate the EPO gene were "obvious" when he first cloned the gene in September, 1983. Defendants have shown that the techniques used to isolate

the monkey cDNA clone were obvious, as evidenced by the approach used at Biogen to isolate the EPO gene. However, the isolation of the monkey CDNA clone occurred based on Dr. Lin's successful isolation of the EPO gene from the human genomic library using nonobvious procedures, and therefore does not render the patent invalid under 35 U.S.C. § 103.

3. Best Mode

Defendants argue that the '008 patent is invalid for failure to comply with the best mode requirement of 35 U.S.C. § 112 because Dr. Lin failed to disclose the best host cells known to him as of November 30, 1984, the date he filed his fourth patent application.

35 U.S.C. § 112 provides in relevant part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, *and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

(Emphasis added).

To constitute adequate disclosure under this provision, a patent specification must set forth both the manner and process of making and using the invention (the enablement rerquirement) *and* the best mode contemplated by the inventor of carrying out the invention (the best mode requirement). *Spectra-Physics, Inc.* v. *Coherent, Inc.*, 827 F.2d 1524, 1532 (Fed. Cir.), *cert. denied*, 484 U.S. 954 (1987) ("*Spectra-*

Physics"). The two requirements are separate and distinct from each other; the essence of the enablement provision is that a specification shall disclose an invention in such manner as will enable one skilled in the art to make and utilize it, whereas the essence of the best mode provision is that the inventor disclose the best mode contemplated by him, as of the time he executes the application, of carrying out his invention. *Id.*, citing *In re Gay*, 309 F.2d 769, 772 (C.C.P.A. 1962). The Federal Circuit explained in *Spectra-Physics*:

> Enablement looks to placing the subject matter of the claims generally in the possession of the public. If, however, the applicant develops specific instrumentalities or techniques which are recognized at the time of filing as the best way of carrying out the invention, then the best mode requirement imposes an obligation to disclose that information to the public as well.

Id.; *see also Dana Corp.* v. *IPC Limited Partnership*, 860 F.2d 415, 419 (Fed. Cir. 1988) *cert. denied*, 109 S.Ct. 2068 (1989).

The *Manual of Patent Examining Procedure*, § 608.01(p)(C) (the "*Manual*"), provides that patent applicants whose inventions depend on the use of microorganisms or other biological material "must take additional steps to comply with the requirements of 35 U.S.C. § 112" when the microorganisms or other biological material are not known and readily available to the public. (DX 957). These additional steps include the making of a deposit of the microorganism or other biological material in a depository that is readily accessible to the public no later than the effective filing date of the application. (*Id.*). The Patent and Trademark Office will also accept the deposit of a

suitable microorganism or other biological material after the effective filing date of the application so long as the microorganism or other biological material is identified in the application as filed and a suitable deposit is made before the patent is granted. (*Id.*).

The cases addressing the deposit requirement have discussed the issue in terms of enablement only without addressing the best mode requirement. *See, e.g., In re Wands*, 858 F.2d 731, 735-36 (Fed. Cir. 1988); *In re Lundak*, 773 F.2d 1216, 1220-21 (Fed. Cir. 1985); *In re Argoudelis*, 434 F.2d 1390, 1392-93 (C.C.P.A. 1970); *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (PTO Bd. Pat. App. & Int. 1986); *Ex parte Jackson*, 217 U.S.P.Q. 804, 806-07 (PTO Bd. App. 1982). *See generally* Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement*, 67 J. Pat. & Trademark Off. Soc'y 569, 607 (1985) ("The deposit requirement is a nonstatutory mechanism for ensuring compliance with the 'enabling' provision under 35 U.S.C. 112.").

The reason given in these cases for the deposit requirement is that where an invention depends on the use of living materials such as microorganisms or cultures, it otherwise "may be impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure." *In re Wands*, 858 F.2d at 735; *see also In re Lundak*, 773 F.2d; at 1220 ("[w]hen an invention relates to a new biological material, the material may not be reproducible even when detailed procedures and a complete taxonomic description are included in the specification"). A deposit will be deemed necessary for enablement where the "starting materials" — the living cells used to practice the invention or cells from which the required cells can be produced — are not readily available to the public. *In re Wands*, 858 F.2d at 735. Even where starting materials are available, a deposit is neces-

sary where it would require undue experimentation to make the cells of the invention from the starting materials. *Id.*

Although the case law does not address the question whether a deposit of the "best mode" is *required* in such cases to satisfy 35 U.S.C. § 112, the *Manual* provision by its express terms draws no distinction between the best mode and enablement provisions and requires deposits to satisfy both requirements.[12] Moreover, it has been held that a deposit may satisfy the best mode requirement. *In re Wands*, 858 F.2d at 736. Although Amgen has argued that § 112 does not require deposits, it does not challenge the PTO's authority to make depositing requirements. *Cf. Animal Legal Defense Fund* v. *Quigg*, 710 F. Supp. 728, 732 (N.D. Cal. 1989) (PTO interpretative rule — that non-naturally occurring, non-human multicellular organisms are patentable subject matter within the scope of 35 U.S.C. § 101 *et seq.* — was promulgated by the PTO within its statutory authority). The purpose of the best mode requirement is to ensure that the public, in exchange for the rights given the inventor under the patent laws, obtains from the inventor a full disclosure of the preferred embodiment of the invention. *Dana Corp.* v. *IPC Limited Partnership*, 860 F.2d 415, 418 (Fed. Cir. 1988), *cert. denied*, 109 S.Ct. 2068 (1989). The requirement that the best mode be described is satisfied when the specification is sufficient to guide one skilled in the art to its

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[12] *See also* PX 341, p. 38 (Statement of Thomas G. Wiseman, Supervisory Primary Examiner for the Biotechnology Group of the PTO, who said "It is probable that a deposit may be needed to meet the best mode requirement."). Defendants objected to the introduction of this document on the ground of hearsay. Plaintiff moved to introduce it to impeach defendants' expert's testimony that deposits of host cells were required in the circumstancese of this case. The court gives the document no weight with respect to the key issue whether deposits were required here because Mr. Wiseman's examples are not clearly applicable to this case, and he did not testify as an expert.

successful application. *Standard Oil Co.* v. *Montedison*, 494 F. Supp. 370, 385 (D. Del. 1980), *aff'd*, 664 F.2d 356 (3d Cir. 1981), *cert. denied*, 456 U.S. 915 (1982). This does not mean, however, that a patentee must disclose data on how to mass-produce the invented product. *Christianson* v. *Colt Industries Operating Corp.*, 822 F.2d 1544, 1562 (Fed. Cir. 1987), *vacated on other grounds*, 486 U.S. 800 (1988) ("the law has never required that a patentee who elects to manufacture its claimed invention must disclose in its patent the dimensions, tolerances, drawings, and other parameters of mass production not necessary to enable one skilled in the art to practice (as distinguished from mass-produce) the invention"); *see also In re Gay*, 309 F.2d 769, 774 (C.C.P.A 1962) ("Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be."); *Standard Oil Co.* v. *Montedison*, 494 F. Supp. at 385.

The specificity of disclosure required to comply with the best mode provision is determined by the knowledge of facts within the possession of the inventor at the time of filing the application. *Spectra-Physics*, 827 F.2d at 1535. Because the best mode provision speaks in terms of the best mode "contemplated by the inventor," there is no objective standard by which to judge the adequacy of a best mode disclosure. *Id.* Instead, only evidence of "concealment," whether accidental or intentional, is considered. *Id.* Because not complying with the best mode requirement amounts to concealing the preferred mode contemplated by the applicant at the time of the filing, in order to find that the best mode requirement is not satisfied, it must be shown that the applicant knew of and concealed a better mode than he disclosed. *Randomex, Inc.*, v. *Scopus Corp.*, 849 F.2d 585, 587 (Fed. Cir. 1988) ("*Randomex*").

Even though there may be a general reference to the best mode, the quality of an applicant's best mode disclosure may be

be so poor as to effectively result in concealment. *Spectra-Physics*, 827 F.2d at 1536; *DeGeorge* v. *Bernier*, 768 F.2d 1318, 1324 (Fed. Cir. 1985). It is not up to the court to decide *how* an inventor should disclose the best mode, but *whether* he has done so adequately under the statute. *Spectra-Physics*, 827 F.2d at 1537.

Is the best mode requirement complied with when an inventor discloses his preferred embodiment indiscriminately with other possible embodiments? 2 D. Chisum, *Patents* § 7.05[1], at 7-78 (1989). The Board of Patent Appeals and Interferences has stated:

> There is no requirement in 35 USC 112 that an applicant point out which of his embodiments he considers his best mode; that the disclosure includes the best mode contemplated by the applicant is enough to satisfy the statute. There is no concealment of best mode here since one of ordinary skill in the art could readily determine the best operating mode.

Ernsthausen v. *Nakayama*, 1 U.S.P.Q.2d 1539, 1549 (PTO Bd. Pat. App. & Int. 1985), *aff'd*, 809 F.2d 787, 788 (Fed. Cir. 1986). In *Randomex*, 849 F.2d at 589, the Federal Circuit agreed with the statement as "applicable to the facts of this case." *But see id.* at 592 (Mayer, J., dissenting) (because the inventor knew that among the disclosed solutions one was the most effective, but only named it as one among many possible solutions, he did not meet the best mode requirement).

Defendants bear the burden of establishing that Amgen failed to set forth the best mode by clear and convincing evidence. *Railroad Dynamics Inc.* v. *A. Stucki Co.*, 727 F.2d 1506, 1517 (Fed. Cir.), *cert. denied*, 469 U.S. 871 (1984).

The question is extremely close whether the best mode was adequately disclosed in the patent specification. Dr. Lin testified that the best mode host cell was disclosed in Example 10 of the '008 patent. (Tr. 5, 19). Example 10 describes expression systems employing CHO DHFR- cells. (PX 2, Col. 26, 11. 44-46). The CHO DHFR- cell, known by its clone name DuX-B11, could be obtained from Dr. Chasin at Columbia University. (Tr. 32, 21).

Example 10 did set forth the steps for transfection of the CHO DHFR cells with plasmids containing the carrier DNA, as well as the DHFR gene necessary for the cells to survive, and for growing the cells in a specified media where only those cells transformed with the DHFR gene, and thereby the EPO gene, would survive. (Tr. 32, 57-58; PX 2, Col. 26, 11. 56-68; Col. 27, 11. 1-4). Example 10 also set forth, as step 3 of the process, a gene amplification technique to amplify DHFR expression, and thereby EPO expression, by using MTX selections. (Tr. 32, 59; PX 2, Col. 27, 11. 27-46). The patent provides that the cells subject to the MTX procedure are a "genetically heterogeneous population." (PX 2, Col. 28, 11. 9-10). Therefore, the final step set forth in Example 10 is the employment of "[s]tandard screening procedures . . . in an attempt to isolate genetically homogeneous clones with the highest production capacity." (*Id.*, 11. 10-13). Dr. Lin testified that this last step meant the use of routine limited dilution cloning procedures. (Tr. 5, 1920).

Dr. Simonsen agreed that Example 10 did discuss the standard procedures of transfection, MTX amplification and limited dilution cloning. (Tr. 33, 26).

Here, defendants concede that the '008 patent would have enabled skilled scientists as of November 30, 1984 to make a host cell yielding some degree of EPO production. (Defendants' Joint Post-Trial Brief, p. 19). Indeed, defendants' own expert, Dr. Christian Simonsen, testified that he had "no doubt"

that with the vectors and sequences, as well as the transfection, gene amplification and limited dilution cloning techniques, described in Example 10 of the patent, someone skilled in the art could generate cell lines expressing some level of EPO, maybe better or maybe worse in terms of EPO production. (Tr. 33, 25-27; *see also* Sadler ITC Dep. Tr. 848).

Relying on the *Manual*, defendants instead argue that Amgen did not satisfy the best mode requirement because it did not deposit any CHO cells, including any cells derived from the CHO B11 3,.1 cell strain, with a publicly accessible repository or identify or describe CHO B11 3,.1 or any of its derivative cell lines in the '008 patent, even though the inventor knew that a selection had been made of a limited number of promising CHO B11 3,.1 cell lines for commercial production prior to the filing of the '008 patent application on November 30, 1984.

Defendants did establish by clear and convincing evidence at trial that Dr. Lin, as head of the EPO project (Tr. 6, 57), knew by November 30, 1984 that the best way to express EPO was from mammalian cells, not yeast cells or E. Coli cells, and that a cell line derived from 11 possible clones from the CHO B11 3,.1 cell strain was to be used for Amgen's master working cell bank which was expected to be started on November 26, 1984. The 11 clones to be developed for the master working cell bank at Amgen were from the CHO B11 3,.1 cell strain, which is scientific short-hand indicating that the host cell resulted from the amplification of CHO DHFR-cells transfected with the plasmid vector pDSVL-gHuEPO and methotrexate selection at the levels of 30, 50 and 100 nanomolars of MTX. (Tr. 32, 53, 97).

Despite this knowledge, Dr. Lin made no deposits when he filed his November 30, 1984 application, having previously deposited on November 21, 1984 only the best E. Coli cell strain and best yeast cell strain without the EPO gene. Approximately 3 years later, one week before the patent issued, on

October 20, 1987, Lin did deposit an E. Coli cell transfected with the monkey cDNA EPO clone and a human EPO clone in "lambda phage," and transmitted a Declaration as to Deposit of Microorganism with the PTO indicating the deposit of two clones, one in an E. Coli host cell. (PX 5).[13] Amgen did not apply for a certificate of correction to the patent to identify the 1987 deposits until April, 1989. *Dr. Lin never deposited any mammalian host cell strain, including any CHO cell, with the ATCC.*

Amgen counters that the patent adequately describes in words the best mode of the invention. The patent describes that cell strain CHO pDSVL-gHuEPO was subjected to a series of increasing MTX concentrations of 30nM, 50nM, 100nM, 200nM, 1 micromolar and 5 micromolar MTX. As of November 30, 1984, the MTX amplification had progressed to 1 micromolar, or 1000 nanomolars. (Tr. 10, 14-15). The patent gave EPO production rates for both the 100 nanomolar MTX-amplified cells and the 1 micromolar-treated cells. (Tr. 10, 16-17; PX 2, Col. 28, 11. 1-8). The cells grown at 100 MTX had an effective production rate of 1264 units per 10 to the 6th cells per 48 hours, whereas the cells grown at 1 micromolar MTX had an effective production rate of 2167 units per 10 to the 6th cells per 48 hours. (PX 303). There is no indication in the patent that the cells grown at 100nM were the preferred host cells, despite Amgen's decision by November 30, 1984 to utilize those cells as opposed to 1 micromolar-treated cells for its master cell bank.

Although plaintiff did not specifically name the cell strain as CHO B11 3.,1 in the patent, it did disclose the best mode in Example 10 of the invention, when it described the production rates of the 100 nanomolar-amplified cells and one micromolar-treated cells. The tough question is whether this disclosure was so inadequate as to effectively amount to concealment.

[13] This document was not stamped as received until November 2, 1987.

First, the patent discloses many embodiments of the claimed invention of a eukaryotic or prokaryotic host cell transfected with the EPO sequence and expressing EPO, but never discloses that the preferred embodiment is the CHO cell. Indeed, Dr. Lin deposited the E. Coli and yeast host cells, which were not transfected, prior to filing the application but did not deposit the preferred embodiment, the mammalian host cell. However, the evidence is clear that EPO is a glycosylated protein which cannot be expressed in a sialated form in prokaryotic cells, like E. Coli and yeast cells. (Tr. 32, 49). Moreover, there were recognized problems with using COS cells to express protein in light of their lack of stability. (*See* p. [A57] *supra*). Therefore, although Amgen did not specify or deposit the preferred mode of embodiment, there is no clear and convincing evidence that one skilled in the art would not understand that CHO host cells as described in Example 10 were the best mode.

Second, while Dr. Lin did not distinguish between cells amplified at 100 nM and 1 micromolar MTX so as to indicate which cell strain was the preferred best mode, the indiscriminate disclosure in this instance of the preferred best mode along with one other possible mode satisfies the best mode requirement. *Randomex*, 849 F.2d at 589.

Defendants argue that the disclosure of the best mode in the patent was inadequate. Dr. Simonsen testified that one following the methods and techniques set forth in Example 10 "may not have been able to reproduce [the] results and most certainly would not have been able to generate cell lines identical to those described later in the PLA, nor would they be able to isolate an identical cell population to that described in the patent, *although what is described in . . . Example 10 . . . you wouldn't know if the properties are the same*." (Tr. 33, 21-22) (emphasis added).

This argument is bolstered by the salient fact that Amgen did not deposit any CHO cell, much less a sample from the

CHO B11 3,.1 cell strain, with the ATCC despite the patent examiner's specific request that a deposit be made. (*See* Tr. 34, 44; DX 207, tab 8, p. 4). Specifically, the patent examiner stated:

> The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an enabling disclosure. The invention depends on certain specific plasmids/microorganisms. As such, a deposit is required under 35 U.S.C. 112.

Although the patent examiner did not specify exactly what was to be deposited, defendants rely on the testimony of Mr. Eugene Rzucidlo, a former patent examiner and a member of the Patent Board of Appeals, who testified that in his opinion the "microorganisms" referred to by the patent examiner meant the host cells. (Tr. 34, 45).

Amgen strenuously argues that it was not required to deposit host cells. However, it has never adequately explained why E. Coli and yeast cells, which are available to the scientific community, were deposited, but not the best mode mammalian cells. The failure to deposit a CHO host cell despite the *Manual* provision and the patent examiner's directive, particularly in light of Amgen's willingness to deposit other kinds of host cells, constitutes evidence of concealment of the best mode.

Nonetheless, the court concludes that the failure to deposit is not enough to constitute clear and convincing evidence of concealment. Unlike the situation in *Spectra-Physics*, as the Simonsen testimony indicates, the details presented concerning the amplification process in Example 10 were sufficient to enable one of ordinary skill in the art to make the best mode of the invention. There is no evidence that Dr. Lin knew of a better mode which he failed to disclose at all. The patent examiner did allow the issuance of the patent after the October 20, 1987, deposits at the ATCC even though the CHO cell was

never deposited. There is no evidence in the record that the patent examiner was misled as to the fact that an E. Coli cell transfected with a monkey cDNA clone and a lambda phage clone were deposited, instead of a CHO cell. (PX 5, Declaration re: Microorganism Deposit, ¶ 3). Therefore, the court has no clear and convincing evidence, despite Mr. Rcuzidlo's testimony as to his own interpretation of the term "microorganism," that the deposit of the CHO cells as opposed to the clone itself, had been ordered by the patent examiner.

Defendants argue that in the absence of "information completely characterizing the cell," it would be highly improbable that a different scientist would select the same cells to clone as Amgen. (DF IV-30). However, they have pointed to no clear and convincing evidence that Amgen had information by November 30, 1984 about other characteristics, which would have better enabled those or ordinary skill in the art to identify the best mode host cell; or that the description of the production rate combined with the amplification procedure was so poor as to effectively constitute concealment.

Rather, defendants argue: "What the patent does not disclose, and given the inherent unpredictability of available techniques *could not* disclose, are the characteristics of host cells which a scientist could reliably reproduce." (Docket 391, p. 5). However, the court declines in the circumstances of this case to hold that the only way to meet the best mode requirement for a transfected host cell is to deposit, although as Dr. Simonsen pointed out, a deposit is "cheap insurance" to ensure this best mode requirement has been met. (Tr. 33, 29). The testimony is clear that no scientist could ever duplicate exactly the best mode used by Amgen, but that those of ordinary skill in the art could produce mammalian host cell strains or lines with similar levels of production identified in Example 10.

Accordingly, the court concludes that defendants have not demonstrated under the clear and convincing evidence standard that the best mode requirement of § 112 has not been met here.

4. Enablement of Claim 7

Defendants contend that claim 7 (and claims 8, 23-27 and 29 which are dependent on claim 7) is invalid under 35 U.S.C. § 112 because it is a single means claim.

Claim 7 of the '008 patent reads:

> A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

Dr. John Wall, Amgen's expert, testified that "sufficiently duplicative" means that it either has the sequence of erythropoietin or is very close to it. (Tr. 2, 30).

A "single means claim" is a claim drafted in "means-plus-function" format yet reciting only a single element instead of a combination. *In Re Hyatt*, 708 F.2d 712, 713 (Fed. Cir. 1983). Paragraph six of § 112 sanctions the use of the means-plus-function format for combination claims only. *Id. See generally O'Reilly* v. *Morse*, 56 U.S. 62, 112-113 (1854); *General Elec. Co.* v. *Wabash Appl. Corp.*, 304 U.S. 364, 371 (1938) ("A patentee may not broaden his product claims by describing the product in terms of function.").

The proper statutory basis for the rejection of a single means claim is the requirement of the first paragraph of 35 U.S.C. § 112 that the enabling disclosure of the specification be commensurate in scope with the claim under consideration. *In re Hyatt*, 708 F.2d at 714. The long-recognized problem with a single means claim is that it covers every conceivable means for achieving the stated result, while the specification discloses

at most only those means known to the inventor. *Id.* Thus, the claim is properly rejected for what used to be known as "undue breadth," but which has since been appreciated as being, more accurately, based on the first paragraph of § 112. *Id.*; *see also In re Borkowski*, 422 F.2d 904, 909 (C.C.P.A. 1970).

GI argues that claim 7 is a single means claim which contains a single element, a DNA sequence, defined only in terms of its properties or function. (Docket 388, p. 20 n. 9). Amgen does not contend that claim 7 is a combination claim but does dispute that it is a single means claim. Amgen also argues that there is nothing wrong with the use of functional language to claim an invention.[14] *See e.g.*, *Rohm & Haas Co.* v. *Dawson Chemical Co.*, 557 F. Supp. 739, 801 (S.D. Tex. 1983), *rev'd on other grounds sub nom. Rohm & Haas Co.* v. *Crystal Chem. Co.*, 722 F.2d 1556 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (where the claimed invention was a method using a chemical compound for selectively killing nearby undesirable plants and had been successfully screened with respect to numerous crops, "[t]he use of functional language to claim an invention is specifically approved by statute, the patent office and the courts, particularly where, as here, it is obviously impossible to enumerate all possible combinations of weeds, crops and application rates or propanil which will produce the recited useful selective, post-emergence activity").

The essential question here is whether the scope of the enablement in claim 7 is as broad as the scope of the claim. *See generally* 2 D. Chisum, *Patents* § 7.03[7][b] (1989). *In re Fisher*, 427 F.2d 833 (C.C.P.A. 1970) ("*Fisher*"), provides a useful analytic framework. That case related to the prepara-

[14] Although Amgen challenges the legal standard asserted by defendants to be applied here, it does not raise any arguments based on the facts. (*See* Amgen's Post-Trial Reply Brief, pp. 6-8).

tion of substances containing adrenocorticotrophic hormones (ACTH) in a composition suitable for injection into human beings in the treatment of certain forms of arthritis and other human pathological conditions. One claim defined the subject matter of the invention as a hormone preparation of certain purity and potency being further characterized as containing a "polypeptide of at least 24 amino acids" with a certain sequence. The court held that the patent application did not enable such a broad claim for the following reason:

> The parent disclosure mentions treating extracts from "hog, beef, lamb, and other animal pituitary glands, and including also pituitary glands of whales." From the instant specification and the Li articles, we know that the hog, beef and lamb ACTHs will contain 39 amino acids, of which the first 24 will be in the recited sequence. We do not know, from the record, the chemical structure of ACTHs of whales or other animals. Appellant's parent application, therefore, discloses no products, inherently or expressly containing *other* than 39 amino acids, yet the claim includes all polypeptides, of the recited potency and purity, having a least 24 amino acids in the chain in the recited sequence. The parent specification does not enable one skilled in the art to make or obtain ACTHs with other than 39 amino acids in the chain, and there has been no showing that one of ordinary skill would have known how to make or obtain such other ACTHs without undue experimentation.

Id. at 836 (emphasis in original).

The court also found that another claim which involved a partially purified ACTH preparation was not enabled by the application, stating:

> It is apparent that such an inventor should be allowed to dominate the future patentable inventions of others where those inventions are based in some way on his teachings. Such improvements, while unobvious from his teachings, are still within his contribution, since the improvement was made possible by his work. It is equally apparent, however, that he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. § 112. That paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. *In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.*

Id. at 839 (emphasis added). *See also Schering Corp.* v. *Gilbert*, 153 F.2d 428, 433 (2d Cir. 1946) ("Claim 4 covers by means of a broad elastic chemical formula . . . not only the compounds illustrated by way of examples in the specifications but also every possible variation of them which might result from further experiment. The specifications do not support that sort of claim but are no more at best than suggestions for experiment. Such experiment might be practically endless and futile as a matter of fact. . . . The claim is for an enormous

number of as yet non-existent compounds and is far broader than any disclosure in the patent."); *Hormone Research Foundation* v. *Genentech, Inc.*, 708 F. Supp. 1096, 1107 (N.D. Cal. 1988) (the breadth of claims supported by a patent's disclosure varies inversely with the degree of unpredictability of the factors involved).

To be enabling under § 112, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. *Atlas Powder Co.* v. *E.I. DuPont de Nemours*, 750 F.2d 1569, 1576 (Fed. Cir. 1984) (where the patent disclosure listed numerous salts, fuels and emulsifiers that could form thousands of emulsions, but no commensurate teaching as to which combination would work, the claim was still enabled because there was a list known to those skilled in the art as to how to select the proper combination). That some experimentation is necessary does not preclude enablement; the amount of experimentation, however, must not be unduly extensive. *Id.* Although it is not the function of claims to specifically exclude inoperative combinations, if the number of such inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. *Id.*

Use of prophetic examples does not automatically make a patent non-enabling. *Id.* at 1577. The burden is on the one challenging validity to show by clear and convincing evidence that the prophetic examples together with other parts of the specification are not enabling. *Id.*

Here, the '008 patent provides: "In addition to naturally-occurring allelic forms of mature EPO, the present invention also embraces other 'EPO products' such as polypeptide analogs of EPO and fragments of 'mature' EPO." (PX 2, Col. 37, 11. 1-4). The patent points out that under published procedures, genes can be designed which differ from mature EPO

in terms of the identity or location of one or more residues. In addition, modifications of the gene may be accomplished by "well-known site-directed mutagenesis techniques." (PX 2, Col. 37, 11. 11-15). These altered genes are called analogs, which have been defined as molecules that have substantially the same biological properties as the native molecules. (Elliott Dep. Tr. 97). The patent describes certain projected analogs. (PX 2, Col. 37, 11. 11-36). None was constructed before the '008 patent application was filed. (Tr. 5, 27, 31). The patent also covers polypeptide fragments duplicating only a part of the continuous amino acid sequence or secondary conformations within mature EPO; which fragments may possess one activity of EPO and not others. (PX 2, Col. 37, 11. 36-41).

In the four to five years since the '008 application was filed, Amgen has engaged in an ongoing EPO analog program headed by Dr. Steven Elliott, who has a PhD from the University of California at Irvine in molecular biology and biochemistry, and began work at Amgen in 1983. (Tr. 9, 7-9; Elliott Dep. Tr. 5). One of the purposes of making EPO analogs is to develop variants of EPO with improved properties, like better biological activity or better stability. (Elliott Dep. Tr. 14). To make one analog requires from a few days to a few weeks. (Elliott Dep. Tr. 29). In four years, Elliott has made 50 to 80 analogs, with *in vitro* specific activity varying over two to three orders of magnitude. (Elliott Dep. Tr. 29, 72). The Elliott analogs have involved replacements, substitutions, and deletions of the amino acids described in the patent. (Elliott Dep. Tr. 189). Over 3,600 different analogs can be made by substituting at only a single amino acid position; and over a million different analogs can be made by substituting three amino acids. (Elliott Dep. Tr. 18-19).

Dr. Elliott testified in a deposition that a scientist might be able to predict the activity of some analogs but not others (Elliott Dep. Tr. 30). He also testified that no one could predict

how many analogs would have increased or decreased activity, but that the majority of analogs would probably not significantly change the activity. (Elliott Dep. Tr. 38). Dr. Elliott said that Amgen had not measured all of the biological properties of the analogs he had made, and he did not know whether the analogs had the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake. (Elliott Dep. Tr. 191-192). Dr. Elliott did not know if any of the plasmids described in the patent (PX 2, Col. 37, 11. 33-35) had this biological property. (Elliott Dep. Tr. 192).

On March 17, 1986, Elliott and Lin prepared a summary of EPO analog work which reported that five synthetic EPO peptides had been created containing portions of the EPO molecule, but that only one had shown any EPO-potentiating activity in the *in vitro* assay; no *in vivo* assay had been conducted. (Elliott Dep. Tr. 94-95; DX 455). Elliott did not know if these molecules were analogs. (Elliott Dep. Tr. 95).

In April, 1989, Dr. Goldwasser testified concerning his work in an ongoing study funded by the National Institutes of Health to modify some of the amino acids in the intact EPO structure to see the result of those modifications on biological activity sites. (Goldwasser Dep. Tr. Vol. II 140.) Scientists have not yet sorted out which particular amino acid residue is required for biological activity, and the data is incomplete. (Goldwasser Dep. Tr. Vol. II 140). Dr. Goldwasser could not testify as to the effect of reagants on certain amino acid residues without empirical study because "[t]here is no theory that tells us what to look for." (Goldwasser Dep. Tr. Vol. II 141).

Based on this evidence, the court concludes that defendants have provided clear and convincing evidence that the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 of the '008 patent without undue experimentation. In making this

determination, the court relies in particular on the lack of predictability in the art, as demonstrated by the testimony of both Dr. Goldwasser and Dr. Elliott. After five years of experimentation, Amgen is still unable to specify which analogs have the biological properties outlined in claim 7. Unlike *Atlas Powder Co.* v. *E. I. DuPont de Nemours, supra*, where those of ordinary skill in the art had a list to select the proper combination of chemicals, here, according to Dr. Goldwasser, there is no theory which tells leading scientists in the field what combination of amino acids will have the biological property claimed in the patent. As stated in *Fisher*, in "cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." 427 F.2d at 839.

This conclusion of non-enablement with respect to claim 7 and the dependent claims is not intended to authorize infringement of the claimed invention in claim 2 by means of insignificant deletions, additions or substitutions of amino acids to the EPO protein which have no substantial effect on the biological activity of EPO. *See Martin* v. *Barber*, 755 F.2d 1564, 1567 (Fed. Cir. 1985) (the doctrine of equivalents allows a finding of infringement when the accused device and the claimed invention "perform substantially the same function in substantially the same way to yield substantially the same result"); *see also Graver Tank & Mfg. Co.* v. *Linde Air Products Co.*, 339 U.S. 605, 609 (1950) ("What constitutes equivalency must be determined against the context of the patent, the prior art, and the particular circumstances of the case. . . . Consideration must be given to the purpose for which an ingredient is used in the patent, the qualities it has when combined with the other ingredients, and the function which it is intended to perform.").

5. Inequitable Conduct

Defendants argue that '008 patent is unenforceable because in prosecuting the '008 patent, Amgen failed to disclose certain information which would have been material to the patent examiner in deciding whether to allow the claims of the patent.

a. The Goldwasser tryptic fragments.

Defendants first claim that Amgen concealed the fact that the tryptic fragments of the EPO gene from which the sequence information was derived were obtained from Dr. Goldwasser and were not made by Amgen. The court, however, concludes that defendants have not established by clear and convincing evidence that there was any material omission or misstatement made by Dr. Lin with intent to mislead or deceive the PTO about the Goldwasser tryptic fragments.

Defendants specifically argue that Amgen misrepresented that Dr. Goldwasser had provided only "*natural* erythropoietin" as contrasted with its in-house scientist, Por Lai, who had assisted in sequencing "*fragments*." (Docket 388, p. 24). The record demonstrates that the statement that "Por H. Lai . . . was a research scientist who assisted in sequencing fragments of the erythropoietin protein" is correct. (Tr. 5, 43; DX 786).

Moreover, although it is true that Goldwasser provided fragments from the natural EPO he possessed, not just natural EPO, there was no showing that this was a material misrepresentation since preparing the fragments was known in the art. (PX 566, Col. 27, 11. 16-25). Defendants also have not demonstrated that the mere preparation of the fragments, without more, constitutes prior art which would invalidate the patent under 35 U.S.C. § 102 (f) and (g) since the invention claimed here is cloning the gene, not preparation of EPO fragments.

Finally, Amgen has claimed that its invention was not obvious because of the use of a large number of mixed fully degenerate oligonucleotide probes to screen a genomic library, not

because of any novel fragmenting or sequencing technique. Regardless of who prepared the fragments, Dr. Lin was the one who selected the T-35 and T-38 fragments, designed the probes based on sequence information obtained by his assistant Por Lai, under his direction, and screened the library. Even if Amgen should have disclosed that fragments of natural EPO were provided by Dr. Goldwasser, defendants have not demonstrated that this omission was intentional since Dr. Lin did not consider it material to what he perceived in good faith to be the invention. The failure to disclose that Dr. Goldwasser had provided the EPO fragments was neither material nor intentional.

b. Number of probes used to isolate the monkey cDNA EPO gene.

Defendants next argue that Amgen misrepresented to the patent examiner that he used 128 probes to screen a cDNA library to isolate the monkey EPO gene. Specifically, Lin stated to the patent examiner:

> More, specifically, Applicant employed two distinct sets of mixed probes to find the human genomic sequence. A first set consisted of a mixture of 128 20-mers. . . . The amino acid sequence which formed the basis for construction of the first set of probes is now known to correspond to residues 46-52 of human erythropoietin. Applicant used *both* the set of 128 20-mers of Table II *and* a second set of 128 17-mers . . . to jointly probe 1,500,000 phage plaques of human genomic library for the human sequence. Three positive clones were isolated. The set of 128 20-mers was thereafter used to successfully screen a 200,000 colony monkey kidney cDNA library, with only seven positive clones being isolated from the 200,000 screened.

(DX 207, tab 15, pp. 16-17) (emphasis in original).

Lin later stated: "To Applicant's knowledge, 128 mixed probes had never before been successfully employed in screening a cDNA library, much less a human genomic library, which is approximately one hundred times more complex than a cDNA library." (DX 207, tab 15, p. 24). Lin also pointed out that a mixture of 128 oligonucleotide probes was "far in excess of 16 or 32 or 48 component mixtures of the Breslow et al. or Woods et al. references." (*Id.*). The *Woods, et al.* reference involved screening a cDNA library with mixtures of probes that were 32-fold and 48-fold degenerate. (*See* p. 49 *supra*). The patent examiner had rejected the cDNA claims, stating that they were unpatentable over these references, and others which teach a monkey source for EPO. (DX 207, tab 13, p. 5).

At trial, Lin admitted he only used a subset of the EpV 128 probes in screening the cDNA library. (Tr. 9, 96). He said there were 16 probes in that mixture, not 128. (Tr. 9, 96). Lin was aware that other persons in the field of cloning had successfully employed as many as 32 probes to isolate genes from a cDNA library. (Tr. 9, 97).

Defendants have presented clear and convincing evidence of a misrepresentation. However, they have not presented clear and convincing evidence that the patent examiner would have considered the misrepresentation important in deciding whether to issue the patent. The primary thrust of Dr. Lin's statement to the patent examiner was the use of 128 probes in screening a genomic library. Dr. Lin did not isolate the monkey cDNA sequence until two or three weeks after cloning the human genomic gene. (Tr. 4, 72). Amgen had already confirmed that the genomic clone isolated was in fact the EPO gene because it was sequenced. (Tr. 4, 74). Lin used a mixture of EpV probes which had already proved successful in isolating the gDNA EPO sequence. He could have attempted initially to screen a monkey cDNA library, instead of a genomic library, to

isolate the monkey mRNA as a way to get the human gene because there was no known human tissue that was enriched in EPO messenger RNA. (Tr. 4, 73). However, he got the human gene "without the hassle of having the monkey gene." (Tr. 4, 73). Because Lin already had isolated the EPO gene, and determined the amino acid sequence, defendants have not demonstrated that the fact that Dr. Lin used a subset of the EpV mixture, as opposed to the full set, would have been material to the patent examiner's determination.

6. Patent Misuse

Defendants argue that the '008 patent is unenforceable because Amgen misused the patent by its commencement of the ITC proceeding against Chugai with knowledge that its claims were without foundation and in an attempt to extend the '008 patent's monopoly. The court concludes that defendants have failed to prove that Amgen's assertion of the '008 patent before the ITC was in bad faith or constitutes patent misuse.

After Amgen filed its first ITC complaint, the Commission voted to institute and investigate under the Tariff Act of 1930, 19 U.S.C. § 1337a, whether there was a violation of the Act in the "unlawful importation of certain recombinant erythropoietin into the United States, or in its sale, by reason of alleged manufacture abroad by a process" which would if practiced in the United States infringe Amgen's patent. (PX 43, p. 2). Amgen contended that the '008 patent covered certain "intra-cellular processes which occur in connection with the manufacture of EPO by transfected host cells," and that the host cell claims in the patent were "unique hybrid claims containing both product and processes." (PX 43, pp. 21-22). Chugai's motion for summary determination was denied. (PX 43, p. 3).

After a period of discovery, and a review of depositions, exhibits and testimony supporting proposed findings of fact, the administrative law judge made an "initial determination"

that the "claims of the '008 patent do not cover a process which is used to manufacture EPO." (PX 43, pp. 60-61). The ITC dismissed the complaint, ruling, among other things, that as a matter of law the '008 claims cannot cover these intracellular processes. (DX 466, pp. 10-11).

The court does not find clear and convincing evidence that Amgen pressed the ITC complaint in bad faith. Defendants argue that the '008 patent claims "are clearly product — not process — claims," and that Amgen knew that the '008 patent did not contain any process claims at the time it made its allegations. (Docket 388, pp. 27-28). However, although Judge Young ruled that the '008 patent does not contain any process claims covering the process of manufacturing recombinant erythropoietin, he recognized it "may well be that the word 'process' in 19 U.S.C. sec. 1337a . . . should be interpreted more broadly than the above interpretation of 'process' made by this Court in the context of patent law." *Amgen*, 706 F. Supp. at 110-111. Amgen's argument concerning the hybrid process and product claims was unique and ultimately was rejected; but the technology involved was novel, and the ITC itself believed it had a sufficient basis for commencing an investigation. It was only after an elaborate fact-finding process that the argument was rejected.

On February 3, 1989, Amgen filed its second complaint with the ITC seeking institution of an investigation pursuant to 19 U.S.C. § 1337 of unfair methods of competition and unfair acts by Chugai in connection with the importation of recombinant EPO into the United States from Japan. (DX 837). It relied on the following statement by the administrative law judge in the "initial determination" on the first complaint:

> There are a number of facts and circumstances established in the record which could justify a broader based investigation. First, it is clear that Chugai entered into a licensing agreement with Genetics Insti-

> tute knowing that Amgen had both cloned the gene first and applied for a patent first. . . . Respondents and the collaborator Genetics Institute were aware of potential patent problems which might hinder their joint venture, and sought to escape from U.S. laws by manufacturing recombinant EPO abroad. . . . Respondents removed transfected host cells from the United States prior to issuance of Amgen's patent to use abroad to produce recombinant EPO with the intent of importing it into the United States.
>
> ****
>
> Since the biotechnology industry is newly emerging . . . and is an important industry for the United States, the Commission may wish to reinstitute this investigation on a different basis, and determine whether there are unfair trade practices involved in respondents (sic) importation of EPO, which may fall short of or not involve patent infringement.

(PX 43, pp. 28, 30).

Although the ITC dismissed the complaint by unanimous vote, Amgen instituted the second complaint as a result of this language in the administrative law judge's opinion. (DX 837). Therefore, defendants have not demonstrated that Amgen instituted the second complaint in bad faith.

B. Infringement

1. GI

GI has not produced any evidence disputing that it has infringed the claims of the '008 patent, and appears not to contest infringement in any of the post-trial memoranda. Accordingly, the court finds that GI has infringed claims 2, 4, 5, 6, 7, 8, 23, 24, 25, 27 and 29 of the '008 patent. (*See* Tr. 2, 26, 29-35).[15]

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[15] Of course, since claims 7, 8, 23, 24, 25, 27 and 29 have been invalidated as non-enabling under 35 U.S.C. § 112, see pp. [A133-A134] *supra*, GI will not be held liable for infringement of those caims.

2. Chugai

Amgen also claims that Chugai has infringed claims 2, 5 and 6 of the '008 patent. It bases its charge of infringement on Chugai Admission No. 155 and the testimony of Dr. Fritsch. Chugai's response to Amgen's Request for Admission No. 155 states in relevant part: "Chugai denies that it has 'shipped' DNA for the purpose of allowing GI to clone that DNA. Chugai admits that it has 'shipped' DNA sequences from its host cells in Japan to GI for the sole purpose of conducting DNA stability studies required by the U.S. FDA." (Docket 286).

David C. Heitz, the executive vice president of G. H. Besselaar Associates ("Besselaar"), testified on behalf of Chugai. Besselaar is in the business of providing clinical development services to its clients seeking the approval of new drugs in the United States. (Tr. 31, 94). In 1987, Chugai asked Besselaar to assist it in the clinical development of EPO. (Tr. 31, 96). Besselaar filed a product license application ("PLA") on behalf of Chugai in September, 1988, which contained clinical information relevant to the safety and efficacy of the new drug EPO in its intended use. (Tr. 31, 97).

The FDA requires DNA stability data in connection with the regulatory approval process. (Tr. 31, 74). Chugai shipped two samples of DNA to GI, which were received on May 3, 1988, so that GI could perform DNA stability studies on Chugai's behalf. (Tr. 31, 75-76). Chugai requested that GI clone the EPO gene and perform DNA sequence analysis to determine the DNA sequence of the EPO coding region. (Tr. 31, 77). The two DNA samples as received were incapable of producing EPO. (Tr. 31, 75). GI did not use any biologically functional vectors as defined in claim 5 of the '008 patent, but only used cloning vectors which would not permit EPO to be expressed. (Tr. 31, 78-79). GI also made no use of any transfected host cells which are described in claim 6 of the '008 patent in connection with the stability studies. (Tr. 31, 79).

GI made no use of the information generated as a result of the stability studies other than send it to Chugai. (Tr. 31, 77-78). Besselaar submitted the stability data to the FDA as part of Chugai's PLA. (Tr. 31, 106).

Based on this evidence, the court concludes that defendants have demonstrated that Chugai's May, 1988 shipment of two DNA samples to GI for the conduct of stability studies was "solely for uses reasonably related to the development and submission of information under" reporting requirements of federal drug laws, which is permitted under 35 U.S.C. § 271(e)(1). *See Scripps Clinic & Research Foundation* v. *Genentech, Inc.*, 666 F. Supp. 1379, 1395-96 (N.D. Cal. 1987), *aff'd in part and modified in part on other grounds on reconsideration*, 678 F. Supp. 1429 (N.D. Cal. 1988) ("The statute's meaning is clear: the use of a patented invention is protected so long as that use is solely for purposes reasonably related to meeting the reporting requirements of federal drug laws.").

Amgen relies on Heitz's testimony that he assumed the information from the EPO stability studies was "useful" as it pertained to the Chugai commercial production process. (Tr. 31, 109). However, Heitz also testified that he had no knowledge as to whether Chugai made any use of the DNA stability study other than for submission to the FDA. (Tr. 31, 108). In addition, Amgen points to the testimony of Dr. Fritsch, who stated that the EPO stability data collected by GI was the "kind of information anyone would like to have," and the fact that Dr. Fritsch's letter transmitting the data to Dr. Tanaka made no mention of the FDA and did not restrict the use of the information in any way. (Tr. 31, 80, 82). However, Dr. Fritsch testified further that the "whole purpose of demonstrating stability was for the purposes of the FDA." (Tr. 31, 82). Chugai stated that this information was used only for the FDA (Response to Amgen's Request for Admission No. 155), and Amgen has introduced no evidence to the contrary.

To support its claim of infringement, Amgen also points to Chugai's response to Request for Admission No. 56, which contains the following admission: "Chugai admits that GI transferred to Chugai, but did not sell, a small quantity of host cells transfected with a cDNA sequence encoding EPO after October 27, 1987. These cells were used by Chugai in Japan for experimental rather than commercial purposes." (Docket 286).

This claim of infringement is without merit for three reasons. First, Amgen did not provide Chugai with any notice in its pretrial statements or supplemental interrogatory responses that it was alleging infringement based on the single host cell transfer, thus precluding any opportunity for Chugai to present evidence in defense. (Docket 238, p. 3 and Ex. A). Second, Amgen has not met its burden of showing that the host cells were manufactured or used in the United States after the issuance of the '008 patent or that the host cells were sold. *Ecodyne Corp.* v. *Croll-Reynolds Engin. Co.*, 491 F. Supp. 194, 197 (D. Conn. 1979) (sale requires payment or promise of payment). Third, Amgen has provided evidence only of one single transfer of host cells and has not demonstrated that this host cell transfer is anything other than a *de minimus* occurrence which does not constitute infringement. *Fife Mfg. Co.* v. *Stanford Engin. Co.*, 299 F.2d 223, 226 (7th Cir. 1962).

3. Willfulness.

Amgen argues that defendants are liable for willful infringement because neither had an opinion of counsel to rely upon before they began to infringe Dr. Lin's claimed invention.

The court concludes that there was no willful, wanton or deliberate infringement here because the validity of the patent was open to honest doubt.

First, Amgen filed four different applications covering the subject matter of the '008 patent and had its claims rejected numerous times by the PTO before the patent was finally issued on October 27, 1987. (DX 805).

Second, GI obtained the oral opinion of inside and outside counsel that the '008 patent was invalid before beginning commercial production of EPO in June, 1988 pursuant to an agreement with Boehringer Mannheim, which had been entered into in 1986, for shipment of rEPO to Europe. (Tr. 29, 89-91). The written opinion from the outside firm was received on July 25, 1988. (DX 820; Tr. 20, 131).

Finally, the PTO declared an interference between the '258 application (representing Dr. Fritsch's work) and the '008 patent. Although this court has ruled against defendants on their anticipation defense, see pp. [A94-A108] *supra*, the declaration of an interference indicates that defendants' defense was not frivolous. Moreover, both the "obviousness" and "best mode" defenses raised close factual and legal questions.

b. '195 Patent

A. Validity

Amgen raises five arguments to support its claim that the '195 patent is invalid, each of which is discussed separately below. As discussed earlier with respect to the '008 patent, see p. [A94] *supra*, Amgen has the burden of proving the patent is invalid by clear and convincing evidence.

1. Anticipation Defense

a. Miyake et al. article.

Amgen argues that the product claims are invalid as anticipated by *Miyake et al.* under 35 U.S.C. § 102(b). Section 102(b) provides that a person shall be entitled to a patent unless "the invention was patented or described in a printed publication in this or a foreign country . . ., more than one year prior to the date of the application for patent in the United States."

It is settled that a party asserting that a patent claim is anticipated must demonstrate, among other things, identity of invention. *Tyler Refrigeration* v. *Kysor Indus. Corp.*, 771

F.2d 687, 689 (Fed. Cir. 1985). Identity of invention is a question of fact and the challenger must demonstrate it by clear and convincing evidence. *Id.* at 689-90. One who seeks such a finding of anticipation must show that each element of the claim in issue is found, either expressly described or under principles of inherency, in a single prior art reference. *Kalman* v. *Kimberly-Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984).

Claim 1 of the '195 patent claims as the invention homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS-PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers. Claim 4 includes the same characteristics except states a specific activity of "at least *about*" (emphasis added) 160,000 IU/AU. The two pharmaceutical composition claims 3 and 6 refer to the same characteristics. (*See* PX 500).

The first element in the claims is that homogeneous EPO has a molecular weight of about 34,000 daltons on SDS-PAGE. GI does not dispute Amgen's argument that the Miyake article anticipates this claimed characteristic of homogeneous EPO. (Docket 391, p. 35). The Miyake article specifies a molecular weight of 39,000 daltons, and Dr. Pierce testified that "about" 34,000 covers the range of 30,000 to 40,000. (Tr. 18, 127-128).

The second element in the claim is that homogeneous EPO moves as a single peak on RP-HPLC. Amgen concedes, as it must, that the Miyake article does not expressly anticipate the claimed invention since RP-HPLC did not even exist in 1977. However, Amgen does claim that this characteristic of movement as a single peak was an "inherent property" of Fraction II derived from the hydroxylapatite ("HT") chromatography of EPO prepared by Miyake on June 30, 1976, which was reported to have a specific activity of 128,620 IU/AU. (PX 528, Table IV).

Amgen relies on a test conducted by Dr. Strickland and witnessed by Dr. Pierce on June 23, 1989 on that fraction which had been frozen in Dr. Goldwasser's laboratory at the University of Chicago. Dr. Pierce testified that 97.08% of the input material in TS Sample 4 moved as a "single peak", and the chromatogram bears that out. (PX 837). No representative of GI was present at any of the experiments. The court allowed the introduction of evidence concerning those tests over defendants' objection.

Only limited reliance on *ex parte* tests is warranted because acts that are not observed or corroborated by an opposing party may be entirely self-serving. *In Re Newman*, 782 F.2d 971, 974 (Fed. Cir. 1986).

The court finds that Amgen has not demonstrated by clear and convincing evidence that an inherent property of Fraction II is that it moved as a single peak. First, the sample tested by Amgen was thirteen years old, and had been stored in Dr. Goldwasser's freezer. (PX 822; Goldwasser Dep. Tr. Vol. II 742). Goldwasser's laboratory had freezer failures, and it is unpredictable what the effect of those failures would be. (Goldwasser Dep. Tr. Vol. II 743).

Second, when Dr. Goldwasser prepared the sample for shipment in 1989, he found some fibrous materials which he removed by centrifugation before sending it to Amgen. (PX 822, Ex. C). Dr. Hewick testified that it was highly likely that EPO and non-EPO proteins in the sample bound to those proteins, and that removal of the fibers would have a larger impact on quantifying the trace components than the major component EPO. (Tr. 21, 100).

Third, the sample amount Dr. Strickland loaded onto the column to do his runs was one-tenth the amount loaded by Dr. Hewick on runs 4 and 5 of shipment 3. (Tr. 21, 88). Loading such a small amount can result in underrepresentation of minor contaminants on the resulting chromatogram. (Tr. 21, 88-89).

Fourth, Dr. Strickland used a different gradient than Dr. Hewick did during the run on Sample 4 upon which Dr. Pierce based his opinion. (Tr. 18, 88-96). Dr. Hewick testified that the change in the gradient for TS Sample 4 resulted in the elongation of the time axis of the chromatogram, making it more difficult to observe contaminants. (Tr. 21, 95-96; 19, 94-96). Dr. Strickland testified that he changed the gradient because he observed an ambiguous area at around 8 minutes which he thought was due to the large jump in acetonitrile concentration, and he couldn't be sure whether there were any contaminants or any other peaks in that area because there was so much discontinuity from the buffer change. (Tr. 14, 167). Although the court does not doubt Dr. Strickland's motives in changing the gradient, this gradient change makes a comparison of Dr. Hewick's runs and Dr. Strickland's much less clear.

The court also finds it noteworthy that Dr. Pierce was not shown the run on TS Sample 3 of HT Fraction II where Dr. Strickland used the same gradient as that used by Dr. Hewick. (DX 870). Dr. Hewick testified that the areas of cotamination were "remarkably consistent" with the runs he had performed. (Tr. 21, 87). Dr. Pierce conceded that there was an "absorbancy of possible significance" from minute 7 ½ to minute 12 on Dr. Strickland's chart of the TS Sample 3 run. (DX 869).

Accordingly, the court finds that Amgen has not demonstrated by clear and convincing evidence based on the 1989 *ex parte* tests that Fraction II had the inherent property of moving as a single peak on RP-HPLC.

The third element in claim one is that homogeneous EPO has a specific activity of at least 160,000 IU/AU. Table IV of the Miyake article only describes "Fraction II as having a specific activity of 128,620 IU/AU. As the patent examiner noted, the characteristic " 'at least 160,000' . . . patentably distinguishes over the highest possible activity reported by Miyake." (PX 501-AC).

A more difficult analysis is required to determine whether the Miyake article anticipates the element of "at least *about*" 160,000 IU/AU in claim 4 because the term "about" is so ambiguous. However, since the Court has found that the single peak is not an inherent characteristic of Fraction II disclosed in the Miyake article, that element of the claim need not be analyzed here but will be analyzed under the defense of indefiniteness. (*See* p. [A167], *infra*).

b. Prior Use.

Pursuant to 35 U.S.C. § 102(a), a person is entitled to a patent unless the "invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." The statutory language, "known or used by others in this country" means knowledge or use which is accessible to the public. *Carella* v. *Starlight Archery & Pro Line Co.*, 804 F.2d 135, 139 (Fed. Cir. 1986), *amended on rehearing*, 1 U.S.P.Q.2d 1209 (Fed Cir. 1986).

Amgen argues that Dr. Goldwasser sent out samples of his pure 1976 uEPO preparations to researchers throughout the country, that these samples were "known by researchers to be pure EPO," and that the "samples were publicly used by the other researchers from at least as early as January, 1978 up to the May, 1984 date of Dr. Hewick's 'discovery' and beyond." (Docket 386, p. 88).

Amgen relies on two samples to support this argument. First, it points to HT Fraction III of the Goldwasser preparation completed July 27, 1976. There was no testimony about this Fraction III in court, and Amgen relies on exhibits and deposition transcripts to show identity of invention. With respect to the two chromatograms run on HT Fraction III in July, 1987 and October, 1988, Dr. Goldwasser never testified that they rose as a single peak and there is no evidence in the record from any of the experts to provide this analysis. (PX 646, 647;

Goldwasser Dep. Tr. Vol. II 43-44, 769-770). As the conflicting testimony of Dr. Hewick and Dr. Pierce indicates, two experts can disagree on the interpretation of these chromatograms as to where the traces indicate contamination, and the court does not have the expertise to make this analysis on its own.

Dr. Goldwasser did testify that there was "only one peak" on the RP-HPLC chromatograph run in February, 1982 on an EPO sample, called native EPO (beta). (PX 645; Goldwasser Dep. Tr. Vol. II 778-780). The court has certain concerns about this testimony. First, Dr. Goldwasser had just received his RP-HPLC equipment, and Amgen has not pointed to any evidence in the record to establish his expertise in reading chromatograms at that point in time. (Goldwasser Dep. Tr. Vol. II 779). Second, there was no testimony as to the gradient used, the time line, the base line or the amount loaded onto the column which all affect the way in which these chromatograms are analyzed. The wavelength on the exhibit PX 645 is 220 nm, but all the testimony in court focused on wavelengths of 280 nm or 214 nm. Indeed, the patent claims specify a wavelength of 280 nm. Further, it is not clear that Fraction III was loaded onto the column, since the exhibit itself refers to the native EPO beta, and Goldwasser's deposition testimony indicates that this native EPO beta is a different sample than HT 7/27/76 Fraction III. (Goldwasser Dep. Tr. Vol. II 778).

Finally, Kung testified that he subjected HT 7/27/76 Fraction III to reverse phase HPLC on July 21, 1987, and that the sample after reverse phase had a specific activity 2.6 times that of the original EPO. (Kung Dep. Tr. 51-52, 66). This testimony indicates that prior to reverse phase, the sample was probably contaminated. Amgen urges the court not to consider this comparison because the "specific activity of the RP-HPLC input material was measured *in vivo* while the output material was measured *in vitro*"; however, the transcript pages cited by

Amgen in support of this argument are confusing and do not clearly demonstrate this, and the exhibit cited as PX 814 does not exist. (Docket 390, p. 36 n.4).

Thus, the court finds that Amgen has not established an identity of invention with respect to that element of the claim asserting movement as a single peak on RP-HPLC.

With respect to the element claiming specific activity of at least 160,000 IU/AU in claim one, Amgen points to Dr. Miyake's deposition testimony that he conducted a bioassay on Fraction III and noted specific activity values of 79,537 and 161,653. (Miyake Dep. Tr. 126). The deposition transcript is unclear as to whether these specific activity values are in IU/AU or u/mg. Because of the "lack of reliability of bioassays," Miyake had conducted two such assays, and then took an average of the two values, which came to an average specific activity of 120,595. (*Id.*). Evidence that one assay of Sample III indicated a specific activity of 161,563, which Miyake himself did not believe was a reliable data point, does not constitute clear and convincing evidence that Fraction III anticipated the element in claim 1 of a specific activity of at least 160,000 IU/AU.

Moreover, as defendants point out, the "EPO Sent Out" list indicates that the EPO sent on January 17, 1978 to Dr. Axelrod, "HT 7-27-76 Fr 3," had a specific activity of 78,000 IU/AU; the EPO sent to Dr. Paul on December 21, 1981, "HT 7-26-76 Fr 3," had a specific activity of 98,910 IU/AU; and the EPO sent to Amgen on December 22, 1982, "HT 7-26-76 Fr 3 Beta EPO," indicated no specific activity value. (PX 649; DX 358). This evidence further refutes Amgen's claim based on Fraction III prepared on July 27, 1976 that the invention was known and used before May, 1984.

In support of its defense of prior use, Amgen argues that HT Fraction II of Dr. Goldwasser's July 26, 1976 uEPO preparation was also sent to researchers around the country, includ-

ing to Dr. Golde in 1979 and 1980. This was the fraction sequenced by Dr. Hewick at Cal Tech in the fall of 1980. However, the "EPO Sent Out" list indicates that the specific activity of the samples sent to Golde was 79,000 IU/AU. There is no evidence in the record that this Fraction II was uncontaminated and moved as a single peak on RP-HPLC. The mere fact that Hewick obtained n-terminal sequence information from this EPO does not indicate it was pure since a partially contaminated sample can yield good sequence information even if there is a large number of minor contaminants. (Tr. 15, 16-21; 37, 35-36). Moreover, Dr. Hewick testified that he did not see a single peak on the chromatogram at Cal Tech, but recollected a fairly high background and a relatively small signal. (Tr. 16, 64-65).

c. Dr. Goldwasser's prior invention.

Pursuant to 35 U.S.C. § 102(g), a person is entitled to a patent unless "before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it." Amgen argues that "homogeneous" EPO was made in Dr. Goldwasser's laboratory in 1976, and that this was a prior invention of the subject matter in the '195 patent product claims. However, Amgen has not shown by clear and convincing evidence that Fraction II or III of the Miyake Sample of June 30, 1976 was homogeneous.

The court will not address Amgen's arguments with respect to the method claims 2 and 5 as these were abandoned by GI prior to trial.

2. Obviousness

Amgen contends that the '195 patent product claims were "obvious" under 35 U.S.C. § 103 at the time the invention was made because in light of the prior art in 1983, "there existed every reasonable expectation for success in using RP-

HPLC for purifying a partially purified EPO preparation which had not previously been subjected to separation from contaminants on the basis of hydrophobicity." (Docket 386, p. 92). The standards for determining the obviousness or nonobviousness of an invention are discussed *supra* at pages [A108-A111]. Defendants apparently do not dispute Amgen's contention that the hypothetical person having ordinary skill in the relevant art is a person with a PhD degree in protein chemistry; with practical experience in the field of protein purification, including the purification of glycoproteins; familiar with standard purification techniques and principles, including RP-HPLC; and with an understanding of bioassays and specific activity measurements of biological substances.

Amgen relies on various articles to support its claim of obviousness. First, it points to an article entitled "A New Preparative Method for Isolation of Human Erythropoietin With Hydrophobic Interaction Chromatography," published by Sylvia Lee-Huang in *Blood* in October, 1980. (PX 534). She reported "[a] new preparative method for isolation of human urinary erythropoietin" using hydrophobic interaction chromatography on "crude urine and urine concentrates from anemic patients . . . without prior manipulation." (PX 534, p. 620). She reported that the prior purification procedures of EPO such as *Miyake et al.*, which separated on the basis of solubility, charge, size and adsorption, were not able to separate EPO from urinary contaminants with similar size, charge and carbohydrate content. (PX 534, p. 623). Her experimental results demonstrated "excellent potential and general applicability" of the hydrophobic interaction chromatography procedure in purifying EPO on the basis of a "different and independent property, hydrophobicity." (*Id.*). She emphasized: "It is especially well suited for initial processing of crude starting material. Urine concentrates and unconcentrated urine samples can be applied directly to the column without any prior treat-

ment." (*Id.*). Although Dr. Huang's technique did not involve high pressure columns, it made use of the same hydrophobic interaction separation principle as RP-HPLC.

Amgen relies on six other articles and abstracts to support its position that it was obvious in 1983 to apply RP-HPLC to purify and separate glycoproteins, including EPO. (PX 541, 540, 543, 544, 545, 546). It also relies on the fact that Dr. Goldwasser applied RP-HPLC to the EPO fractions prepared in 1976 and in February, 1982 as soon as he received his first RP-HPLC equipment.

Amgen has provided clear and convincing evidence that in 1983 it was obvious to apply RP-HPLC to separate and purify glycoproteins. However, it was not obvious to apply RP-HPLC to EPO prepared by the *Miyake et al.* procedures because the undisputed evidence is that the scientific community believed that material to be pure already. (PX 545; *see* p. [A84] *supra*). Although Dr. Goldwasser had used RP-HPLC as an "analytical step" beginning in 1982, Dr. Goldwasser's laboratory did not use RP-HPLC as a final purification step until 1987. (Kung Dep. Tr. 109-12; Goldwasser Dep. Tr. Vol. II 433-436; DX 385). Indeed, it is noteworthy that Goldwasser used RP-HPLC in 1982 on EPO prepared in 1976, and interpreted the chromatogram as rising in a single peak, see p. [A155] *supra*. Apparently believing that the *Miyake et al.* procedures adequately purified EPO, he did not institute RP-HPLC in his laboratory until 1987. Amgen does not explain why RP-HPLC was instituted in 1987, and the court can only infer that Dr. Goldwasser concluded at that point that RP-HPLC would further purify the EPO he had once believed was already pure.

Dr. Pierce testified that it would be obvious to apply RP-HPLC even to material which had been reported in the art as already purified to apparent homogeneity. He said: "In this case with any biologically active substance, biologically active protein, particularly when no structural — significant structural

information was available at that time, it would be absolutely ridiculous when a new technique like that comes along not to apply it even to material of apparent homogeneity." (Tr. 19, 21). This testimony is not persuasive for the following reasons. First, there is no evidence that anyone in fact applied RP-HPLC to further purify urinary EPO already purified by the *Miyake et al.* methods until May, 1984 when Dr. Hewick did it. Indeed, Dr. Strickland, Amgen's scientist working on the purification of uEPO, who was quite familiar with RP-HPLC, did not use RP-HPLC in mid-1984 to further purify uEPO which already had been purified according to a modified Goldwasser procedure. (Tr. 14, 66-67). Second, Dr. Pierce did not testify that it was obvious to use RP-HPLC as a purification step when the material was already thought pure, but rather as an analytical tool concerning a protein about which there was little significant structural information. Further, there is no evidence that an ordinary person skilled in the art in 1984 would have read a chromatogram of EPO subjected to the *Miyake et al.* procedures; would have concluded, as did Dr. Hewick, that the EPO was only partially pure; and then would have prepared homogeneous EPO with the characteristics in claim 1.

The articles and abstracts that Amgen relies on demonstrate attempts to apply RP-HPLC to purify EPO from crude urinary starting materials which had not been purified by the Miyake procedures. None of the abstracts reports a specific activity higher than Miyake's or purports to have purified EPO to homogeneity. (Tr. 19, 120-121). For example, PX 546 showed a procedure for the purification of EPO from the urine of patients suffering from certain anemias using RP-HPLC as a step, which resulted in specific activity of approximately 40,000 u/mg. PX 544 reported the "rapid preparation of human urinary erythropoietin by high performance liquid chromatography," using urine from a patient with aplastic anemia, resulting in a specific activity of only 16,800 u/mg.

Amgen has not demonstrated by clear and convincing evidence that there was anything in the prior art to suggest the desirability of applying RP-HPLC to *Miyake et al.* EPO preparations, or that there was anything in the prior art which would have made the subject matter of the claimed invention — in particular, the claim of specific activity of at least 160,000 IU/AU, and movement as a single peak on RP-HPLC — obvious to a person skilled in the art in 1984.

3. Indefiniteness

35 U.S.C. § 112 provides in relevant part: "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."

"The statutory requirement of particularity and distinctness in claims is met only when they clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." *United Carbon Co.* v. *Binney & Smith Co.*, 317 U.S. 228, 236 (1942). "A zone of uncertainty which enterprise and experimentation many enter only at the risk of infringement claims would discourage invention only a little less than unequivocal foreclosure of the field." *Id.*

A decision on whether a claim is invalid under this provision requires a determination of whether those skilled in the art would understand what is claimed when the claim is read in light of specification. *Seattle Box Co.* v. *Industrial Crating & Packing*, 731 F.2d 818, 826 (Fed. Cir. 1984). If the claims, read in light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more. *Shatterproof Glass Corp.* v. *Libbey-Owens Ford Co.*, 758 F.2d 613, 624 (Fed. Cir. 1985).

Claims are not rendered indefinite by the use of relative terms so long as one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification. *Seattle Box. Co.* v. *Industrial Crating & Packing, Inc.*, 731 F.2d at 826 ("substantially equal to"); *Rosemount, Inc.* v. *Beckman Instruments, Inc.*, 727 F.2d 1540, 1547 (Fed. Cir. 1984) ("close proximity"); *In re Marosi*, 710 F.2d 799, 802 (Fed Cir. 1983) ("essentially free of"). *But cf. United Carbon Co.* v. *Binney & Smith Co.*, 317 U.S. at 234 (". . . what on first impression appears to be a reasonable certainty of dimension disappears when we learn that 'approximately one-sixteenth of an inch in diameter' includes a variation from approximately ¼th to ⅒oth of an inch").

Amgen argues that the criteria for determining "homogeneous" EPO are vague. First, it contends that the patent and prosecution record is silent as to what range is covered by "about" 34,000 daltons on SDS-PAGE. However, Amgen has not demonstrated that this term is indefinite to those skilled in the art. Dr. Pierce testified that in the context of the weight of a glycoprotein measured on SDS-PAGE analysis, the word "about" would mean a range of values from 30,000 to 40,000 daltons on SDS-PAGE gel analysis. (Tr. 18, 128; PX 812, p. 49). Amgen points out that on Chugai's IND application, the molecular weight is specified as 32,000 to 42,000. (PX 809, p. 1). However, there is nothing in the record which shows that the difference of 2,000 daltons in the context of a glycoprotein on SDS-PAGE analysis is material.

Next, Amgen argues that the term "single peak" is indefinite. However, Dr. Pierce testified that his understanding of the characterizing factor "movement as a single peak on reverse-phase HPLC" is "that the tracing is primarily or essentially moving as a symmetrical peak but there are shoulders or inflection." (Tr. 18, 129). He also described the peak to the right of 30 minutes on Figure 1 of the '195 patent as rising as a "single

peak." (Tr. 18, 129-130). Amgen itself used the term "single peak" to describe its own EPO in its literature. *Amgen*, 706 F. Supp. at 102.

Amgen argues that certain chromatograms in the Chugai IND application "clearly" are not made up of single peaks, and indeed there appears to be a second small peak immediately adjacent to the large peak in these chromatograms. (PX 809, pp. 274-276). However, Amgen points to no expert testimony concerning these chromatograms, and therefore the court does not find them to be clear and convincing evidence of indefiniteness.

Third, Amgen argues that the characteristic of "a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers" is indefinite in a number of respects. Amgen points out that the patent is silent as to how specific activity is to be measured: whether by *in vivo* or *in vitro* assay. With respect to uEPO, Dr. Hewick testified that since the procedures in the patent are designed to eliminate desialation, "there should be good correspondence between the in vitro and in vivo assay." (Tr. 13, 28; PX 500, Col 7, 11. 53-56). The patent describes two kinds of *in vitro* assays which can be used to quantify EPO. (Tr. 13, 28).

With respect to rEPO, Dr. Fritsch testified that the *in vivo* and *in vitro* assays yielded nearly identical results. (Tr. 24, 174). Although Amgen points to some data which did not show identical results with respect to *in vivo* and *in vitro* tests for rEPO (PX 791), Dr. Fritsch explained that the best data comparing results from *in vitro* and *in vivo* assays from five different production batches showed a one-to-one ratio. (Tr. 30, 62-63).

Amgen argues that the assumption that there is a one-to-one correlation between *in vitro* and *in vivo* assay data is incorrect and in fact the *in vitro* assay values for uEPO are inherently higher than its *in vivo* assay values. (AF 1091). Amgen relies

on Chugai's IND application which states: "The *in vivo* specific activity of the highly purified urinary EPO appears to be approximately 65% that of recombinant EPO while the *in vitro* specific activity (6.1.2.4.B) of urinary EPO appears identical to recombinant EPO." (PX 811, p. 984). This document indicates that the specific activity of highly purified uEPO differs depending on whether it is measured by *in vivo* or *in vitro* bioassays, and does seem to contradict Hewick's testimony that it is immaterial whether the specific activity of uEPO is measured by *in vitro* or *in vivo* activity.

Certainly, it is "curious", to use use Dr. Fritsch's expression, that the patent did not specify whether the claim covered 160,000 IU/AU specific activity as measured by *in vivo* or *in vitro* bioassays. Although the evidence establishes that there is a one-to-one correspondence between the *in vitro* and *in vivo* bioassays for rEPO, the IND application indicates a material difference with respect to uEPO. However, Dr. Fritsch, Dr. Hewick and Amgen's expert Dr. Pierce all agreed that the bioactivity of EPO had to be measured by *in vivo* testing because that is the only valid way of assaying material that is proposed to be used therapeutically. (Tr. 19, 11; 13, 29; 30, 70). In light of the fact that all the experts testified that an *in vivo* activity measurement was ultimately required to determine the specific activity, Amgen has not produced clear and convincing evidence that this element of the claim is indefinite to one of ordinary skill in the art.

Finally, Amgen argues that the '195 claims are indefinite with respect to the terms "at least" and "at least about" 160,000 IU/AU. However, Amgen has not demonstrated that those skilled in the art do not recognize a range of assay variability when putting a value on a particular specific activity. Indeed, the evidence is to the contrary.

Dr. Jaime Caro, a professor of medicine at Thomas Jefferson University in Philadelphia, has over twenty years of experience

in conducting EPO bioassays by *in vivo* and *in vitro* tests, and worked as a consultant doing *in vivo* bioassays for GI and Chugai. He testified that the range of variation for *in vivo* specific activity data for EPO "could be up to 20 per cent." (Caro Dep. Tr. 29). Caro testified that the variability is "mostly due to the fact that this is a biological assay that uses live animals as compared to chemical assays. Animals vary; they range." (Caro Dep. Tr. 23). When Caro reports the results of the *in vivo* bioassay work to GI, he does not give a range of variation for the particular sample assayed, but instead calculates a mean. (Caro Dep. Tr. 24).

Dr. Fritsch testified that the range of error for the *in vivo* bioassays of rEPO was a little bit under 25%. (Tr. 24, 176). He reported a range of 20 to 30 per cent to the patent examiner in the summer of 1986. (Tr. 24, 177). Dr. Michael A. Recny, who was the head of GI's structural protein chemistry lab and responsible for the biochemical characterization of rEPO and uEPO, testified that the generally accepted standard deviation for the *in vivo* biological assay is about 20 to 25 per cent. (Recny Dep. Tr. 28). He testified that the same standard deviation applied to the *in vitro* assay technique used by Krystal as disclosed in the patent. (Recny Dep. Tr. 30; PX 500, Col. 7, 11. 53-56).

Dr. Pierce, Amgen's own expert, testified that a protein chemist or a person with ordinary skill in the bioassay field, would look at a specific activity figure and know that there would be a range of error. (Tr. 19, 159-160). Dr. Pierce also testified that biological activity in his experience is only one criterion of purity and a criterion which is not "very rigid or very desirable." (Tr. 19, 162). He believed that conducting a bioassay was "rather dicey," and not of much value unless a series of assays were conducted. (Tr. 19, 117).

Dr. Fritsch also testified about the difficulty in developing a bioassay protocol to give reliable specific activity data at GI. (Tr. 24, 172-173).

An *in vivo* bioassay in which EPO is injected into living beings, like mice, looks at the incorporation of iron into reticulocytes. (Tr. 24, 148). This incorporation in a particular mouse is measured against a standard measurement of activity. (Tr. 24, 147-148). Dr. Fritsch testified that there are three kinds of data used in conducting bioassays: "sample data"; the "best estimate of the true mean"; and the "true mean." (Tr. 24, 169-170). If a scientist has a protein which is put into a bioassay to measure the specific activity, the resulting sample data will not necessarily be the actual mean activity of that sample because of the variation in bioassays conducted on living animals. (Tr. 24, 171). The "true mean" would be the specific activity of EPO if a scientist could measure it an infinite number of times. (Tr. 24, 158-159). "The best estimate of the true mean" would be the value that could be obtained based on all the available data. (Tr. 24, 159).

A person of ordinary skill in the art would understand the figures 70,400 u/mg and 82,720 IU/AU in the Miyake article (PX 528) to be the best estimate of the true mean potency of EPO. (Tr. 24, 168-170). Subsequent authors reported the specific activity of EPO to be 70,400 u/mg, without indicating this figure was a mean or that it carried a range of error. (PX 536, 531). An experienced scientist would not rely on 128,620 as a mean value because that was the specific activity value for an individual sample within a normal range of variation from the true mean. (Tr. 24, 169).

GI has demonstrated that those skilled in the art would understand the specific activity value of 160,000 IU/AU in the '195 patent to refer to the best estimate of the true mean potency of EPO. (Tr. 24, 170).

The fact that GI does not specify a range of error does not render the claim to "at least" 160,000 fatally indefinite. In its own product specification, Amgen's EPO is described as greater than 160,000 units; this value is not identified as a mean and

does not provide a standard deviation or range of error. (PX 525, Ex. C; DX 214).

Amgen relies on an internal document from Jeffrey Browne, PhD, the head of Amgen's molecular cell biology department, to the vice-president of Amgen's exclusive licensee Ortho Pharmaceutical Corporation, which reports an average specific activity value and a range of error of 19 percent to support its argument that a range of error should be specified. (DX 889). However, that document was written expressly to compare GI's and Amgen's rHuEPO, and was not for scientific publication. It points out that the measurement of the *in vivo* biological activity is "far from precise." (DX 889). Amgen also relies on an article published by its scientists which reports a range of error in bioassays. (DX 323, p. 217). However, other leading scientists, including Amgen's own Dr. Strickland, have reported specific activity values without reporting that range of error. (*See* PX 528, 531, 536; Tr. 14, 95-96). Accordingly, the documents cited by Amgen do not refute by clear and convincing evidence defendants' contention that a person of ordinary skill in the art would understand 160,000 IU/AU to denote a mean value with a range of error between twenty and thirty percent, the range reported to the patent examiner.

Whether the term "at least *about* 160,000" (emphasis added) is indefinite poses a much closer question. Judge Young did not address this question as GI relied on evidence that the potency of Amgen's EPO was greater than 160,000. *Amgen*, 706 F. Supp. at 103. There is not dispute that bioassays provide an imprecise form of measurement with a range of error. Although GI has persuasively demonstrated that a person of ordinary skill in the art would understand 160,000 to refer to a mean potency with a range of error, the term "about" 160,000 gives no hint as to which mean value between the *Miyake et al.* value of 128,620 and the mean specific activity level of 160,000 constitutes infringement.

There is no evidence that Amgen, GI or any of the prior art references has used the term "about" in describing the potency of EPO. Rather, the scientific literature either places a value on specific activity which those of ordinary skill in the art understand to be a mean with a certain range of error or it provides a specific activity value specifying the range of error in terms of percentages or specific values. *Compare* PX 579, p. 809 and DX 323, p. 217 (citing specific range of error values) *with* PX 536, p. 488 and PX 531, p. 3651 (citing only mean value). Chugai's own documents reflect the difficulties created by the word "about." On March 25, 1987, Chugai's International Development Department reported that Chugai's then product current value for EPO was 138,000 IU/AU, and then stated: "Problematic Point: Based on ambiguities of in vivo activity and glucoprotein (sic) measurements, it is difficult to anticipate the impact." (PX 884).

The history of the patent application for the '195 patent sheds some light on the genesis of the word "about". On or about January 15, 1987, the patent examiner did not allow the broader claim originally asserted by defendants of specific activity of "at least 120,000" because of "the disclosure in Miyake at p. 5561, Table IV, fraction II which shows a product with a U/A of 128,620." (PX 518). On January 16, 1987, Patent Examiner Schain and attorney Eugene Moroz had a telephone conference about the addition of three claims which basically "track the previously allowed claims except for the presence of the word 'about' before the term '160,000 IU per absorbance unit at 280 nanometers.'" (PX 501-AF). Chugai's attorney, Eugene Moroz, explained the addition of the word "about" in the document entitled "Amendment under 37 CFR 1.312" submitted to the PTO on February 10, 1987 as follows:

> In the aforesaid January 16, 1987 telephone conference, the Examiner indicated his willingness to allow such claims on the following bases:

> (1) At page 15 of the specification, it is stated: "The EPO protein eluded by RP HPLC is about twice as pure as the material eluded from the hydroxylapatite column (STEP E)". The aforesaid disclosure is supportive of the phrase "about 160,000 IU per absorbance unit at 280 nanometers."
>
> (2) Further support for the aforesaid phrase is found in the specification at pages 4 and 6 which discloses a specific activity of at least 120,000 IU per absorbance unit at 280 nanometers, and more preferably 160,000 IU.
>
> It is respectfully submitted that claims 27, 28 and 29 presented herein, are supported by the teachings of the specification, do not constitute new matter and comprise subject matter to which applicant is dully entitled.

(PX 501-AF).

However, Dr. Hewick testified that the area under the EPO peak was less than 50 percent of the total proteins present in the sample as calculated by using the technique of cutting and weighing the areas above the baseline on the chromatograph; he concluded from this that the specific activity of EPO would be *more* than twice the 83,000 specific activity value provided by Miyake. (Tr. 15, 175-177; Tr. 12, 77, 88; PX 501-W, ¶ 7; PX 501-T, ¶ 6). The last minute addition of the word "about" seems to constitute an effort to recapture as a claimed specific activity a mean activity somewhere between 120,000, which the patent examiner found was anticipated by the prior art, and 160,000 IU/AU.

If the term "about" is intended to reflect the concept that 160,000 IU/AU is a mean value with a range of error, it is redundant with respect to claim one, as explained by defendants. Unfortunately, neither of the parties focused on the dif-

ferences between what claim one and four encompassed as the claimed invention. Particularly in light of the inherent imprecision in quantifying specific activity by bioassay, the fact that "at least 160,000" already reflects a range of error between 20 and 30 percent as recognized by the scientific community, that no other scientific publication seems to use the word "about" in reference to specific activity, and that Chugai itself seemed unclear as to whether its 138,000 product value for EPO was encompassed by the claimed invention, the court finds that there is clear and convincing evidence that claim 4 and claim 6, which incorporates the claimed invetion of claim 4 by reference, are indefinite and do not clearly circumscribe what is foreclosed from future enterprise. *United Carbon Co.* v. *Binney & Smith Co.*, 317 U.S. at 236.

4. Unenforceability

Amgen contends that the patent is rendered permanently unenforceable because defendants violated 37 C.F.R. § 1.56 which imposes a duty of candor and good faith on an inventor and each attorney or agent who prepares or prosecutes a patent application toward the PTO, and a duty to "disclose to the Office information they are aware of which is material to the examination of the application." Section 1.56 further provides: "Such information is material where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent."

The essential elements in any proof of fraud or inequitable conduct include intent and materiality. *Rohm & Haas Co.* v. *Owens-Corning Fiberglas Corp.*; 196 U.S.P.Q. 726, 743 (N.D. Ala. 1977). A patent should not be held invalid or unenforceable for less than an intentional misrepresentation to the examiner, but for which the patent application would not have been allowed. *Id.* Materiality is not merely relevance but rather is directed to facts which would have or should have altered the examiner's decision to allow the application. *Id.*

(a) Amgen argues that defendants failed to disclose the inoperativeness of Example 2. However, that was disclosed in the '195 patent. (PX 500, Col. 8, 11. 43, 44).

(b) Amgen argues that defendants failed to disclose that Example 2, dealing with purification of rEPO, was deleted from the PCT application. However, Amgen has provided no explanation as to why omitting to tell the examiner of this deletion would have affected his decision since the claimed invention in the PCT application was the same. If anything, one could argue that the deletion of Example 2 from the patent application would have constituted an omission of a material fact. The admission of failure in purifying rEPO was a reflection of candor, not duplicity.

(c) Amgen criticizes GI for not revealing that *Miyake et al.* discloses a uEPO product having a specific activity of 128,620 u/AU. Amgen correctly points out that this is material since GI's claims, as initially worded, contained a specific activity limitation of "at least 120,000" u/AU, and since the patent examiner found this claim invalid as anticipated by the 128,620 specific activity value in *Miyake et al.* Dr. Hewick knew of this specific activity value. (Tr. 12, 7-8).

The court finds that Amgen has not met its heavy burden of showing by clear, unequivocal and convincing evidence any fraud or inequitable conduct. *Kangaroos U.S.A., Inc.* v. *Caldor, Inc.*, 778 F.2d 1571, 1576 (Fed. Cir. 1985). First, GI did bring the Miyake article to the patent examiner's attention, even if it did not specifically point out the 128,620 specific activity figure in Table IV. Second, the Miyake paper itself reports a mean potency of 82,720 IU/AU for two of the fragments of EPO purified by the seven-step procedure, and the introductory abstract discusses a potency of 70,400 u/mg. (PX 528, pp. 5558 and 5562). Although, *Miyake et al.* does refer to the specific activity value of 70,400 u/mg as a "minimal potency" in the discussion section of the article (PX 528,

p. 5563), other scientists of ordinary skill in the art similarly interpreted the Miyake article as reporting a 70,400 u/mg potency value for EPO, and did not mention the 128,620 figure. (*See, e.g.*, PX 531, 536; Tr. 14, 95). As Dr. Fritsch testified, one with ordinary skill in the art might have fairly interpreted the 128,620 figure as a single sample data point, rather than a best estimate of the potency of EPO. (Tr. 24, 169-170). Thus, although it would have been preferable to have highlighted the 128,620 figure to the patent examiner, Dr. Hewick did not engage in inequitable or fraudulent conduct in failing to do so.

(d) Amgen argues that GI failed to disclose that the range of assay variations was plus or minus 20-30 percent, but the record refutes this claim. Dr. Fritsch told the patent examiner that bioassays had a reasonably high standard of error relative to other physical types of measurements, and that the standard error was in the range of 20 to 30 percent. (Tr. 24, 88-89, 173-177).

(e) Amgen points out that the examiner was not aware of the public distribution of Dr. Goldwasser's uEPO in the 1978-1983 time period. However, Amgen has not provided clear and convincing evidence that this uEPO was homogeneous, and therefore this omission is not material. (*See* pp. 133-142 *supra*).

(f) Amgen argues the GI engaged in a "blatant and knowing misrepresentation" of material facts by failing to disclose that the actual assay data for uEPO or for rEPO available to GI in November, 1986 did not support the claims to "homogeneous" EPO having a specific activity of at least 160,000 IU/AU. On November 6, 1986, the patent examiner asked for "[a]n explanation of just how the Hewick data supports [all pending] claims 21-24" in order "to evaluate the declaration under 37 CFR 1.131." (PX 501-AB). On November 11, 1986, Eugene Moroz submitted a "record of interview" which described the

interview with the patent examiner that took place on October 31, 1986. (PX 501-Z). During the interview, Dr. Fritsch and counsel discussed that Kirin-Amgen patent application and whether the Hewick Declaration established a date of invention earlier than Kirin-Amgen's earliest date of disclosure (November 30, 1984), the Lee-Huang patent application, and another GI patent application. The patent examiner suggested that the applicant "annotate" the earlier Fritsch and Hewick Declarations. (PX 501-Z).

Hewick submitted a supplemental declaration which explained how he calculated the actual specific activity of EPO. In this declaration, he also stated that he reached his conclusions prior to November 30, 1984. (PX 501-W). The earlier declaration had not explained how these calculations were done. (PX 501-T). The examiner did not request bioassay information, and there is no information in the record that GI misrepresented the existence or values of existing bioassay information.

The harder question is whether GI failed to disclose material information regardless of whether or not the patent examiner actually asked for it. Amgen argues that GI should have disclosed certain information submitted on November 5, 1986 by Chugai in an IND application to the FDA that GI had purified uEPO by applying RP-HPLC to a partially purified product and had reported an *in vivo* specific activity of 109,000 plus or minus 28,000 IU/AU (PX 811, pp. 978, 985). (Docket 386, p. 102).

The data in the IND application is not so clear-cut. It discloses that the average *in vitro* specific activity of uEPO is 218,000 plus or minus 21,000 units/mg; divided by the extinction coefficient of 1.31, this average value amounts to approximately 166,412 IU/AU. (PX 811, p. 983). It also reports the average *in vivo* specific activity of human urinary EPO as 143,000 plus or minus 37,000 units/mg; this average value amounts to

approximately 109,000 after dividing by the extinction coefficient. Chugai explained:

> The *in vivo* specific activity of the highly purified urinary EPO appears to be approximately 65% that of recombinant EPO while the *in vitro* specific activity (6.1.2.4.B) of urinary EPO appears identical to recombinant EPO. This implies that the urinary protein is capable of eliciting the same biological effect on responsive cells but it may be inactivated or cleared more rapidly than recombinant EPO when injected into a living animal. It is well known that the *in vivo* biological activity of glycoproteins is affected by the extent to which the carbohydrate chains are capped with sialic acid. Proteins containing uncapped chains are much more rapidly cleared from the bloodstream than fully sialated glycoproteins and therefore have reduced activity. Since urinary EPO is purified from much cruder starting material than recombinant EPO, it is probable that urinary EPO is more exposed to the neuraminidase enzymes which can desialate glycoproteins. This may well explain the reduced *in vivo* activity of the urinary EPO.

(PX 811, p. 984).

On June 15, 1987, Chugai reported to the FDA that rEPO displayed an *in vivo* specific activity greater than 200,000 units/mg polypeptide, in contrast to the 132,000 units/mg *in vivo* specific activity for uEPO. (PX 812, p. 1051). Chugai again noted it was not surprising to observe that rEPO is of

higher *in vivo* specific activity than uEPO because "EPO purified from pooled urine has been excreted through the kidney and therefore exposed to a variety of enzymes that could conceivably degrade the native protein and affect its *in vivo* efficacy." (PX 812, p. 1052).

This is a most troublesome point. All the experts agree that the claims in the patent to a specific activity of 160,000 IU/AU should be measured by the *in vivo* method. Yet, there is evidence in the IND application that the *in vivo* tests for uEPO in November, 1986 yielded results of 109,000 IU/AU. The *in vitro* tests of uEPO, and the *in vitro* and *in vivo* tests of rEPO, yielded results over 160,000 IU/AU.

The issue is even further confused by the fact that Amgen's own scientists conducted *in vivo* and *in vitro* tests and a RIA, which measures immunoreactivity, to compare rEPO and uEPO and concluded: "These experiments indicate that the human urinary and recombinant EPO are indistinguishable in the parameters of biological and immunological reactivity that can be measured by these assay systems." (DX 323, pp. 217-218).

Unfortunately, Amgen has not pointed the court to any testimony which would clear up the confusion from the conflicting evidence in the record, and therefore has not provided clear and convincing evidence that there is a substantial likelihood that the failure to disclose the *in vivo* test results of uEPO in the IND application would have affected the patent examiner's decision to issue the patent.

(g) Amgen also argues that Dr. Hewick failed to disclose certain computations which showed a higher calculated value for the specific activity of EPO. (PX 515). However, these calculations were made by Dr. Fritsch, and Dr. Hewick neither saw them nor recalls discussing them. (Tr. 12, 95). Moreover, since the values were higher than 160,000, Amgen has not demonstrated why there is a substantial likelihood that the calculations would have affected the patent examiner's decision-making.

(h) Amgen argues that GI improperly failed to disclose that actual bioassay data available in November, 1986 showed *in vivo* specific activity levels less than 160,000 IU/AU. Amgen relies on certain specific activity data generated in June, 1986, which indicate that the mean specific *in vivo* activity of rEPO was less than 160,000 in four out of seven samples. (PX 778). Other data from early 1986 indicate similar results. (PX 786; Tr. 30, 56). However, Amgen has failed to demonstrate any fraudulent intent or inequitable behavior since Dr. Fritsch testified that when he became directly involved in the project as of October, 1986, at the time GI's documentation was sent to Chugai, GI looked at the sum of all the data with respect to *in vitro* and *in vivo* analysis and found specific activity values over 160,000 IU/AU. (Tr. 30, 60).

Amgen also points out that Chugai determined that the potency value of its rEPO was 138,000 IU/AU in a report to the FDA. (PX 809, p. 212). On June 5, 1987, Chugai submitted IND application documents to the FDA which reported: "The mean potency value resulting from this computation was 180 x 10 [to the third power] IU/mg EPOCH polypetide." (PX 809, p. 206). However, Fritsch had never seen this report or heard of those values. (Tr. 30, 50-51). These values were sent to the FDA just three weeks before the patent issued on June 30, 1987. Dr. Fritsch testified he could not discuss the Chugai data because in the past Chugai had used a different method for estimating protein concentration which gave lower specific activity figures, and he did not know which form of protein concentration measurement was used to generate the specific activity values in PX 809. (Tr. 30, 51-52).

Moreover, Amgen's reliance on this submission is undercut by Chugai's FDA submission ten days later reporting specific activity levels higher than 160,000 by both GI and Chugai. (PX 812, pp. 95-97). In any event, even if the 138,000 IU/AU potency value were material, there is no evidence that Dr.

Hewick, or indeed anyone at GI, had seen Chugai's specific activity value of 138,000 IU/AU in time to report it to the patent examiner; therefore, Amgen has failed to meet its burden of proof on intent.

(i) Amgen argues that GI should have disclosed that rEPO could be purified to 90 per cent purity without the use of RP-HPLC. On November 25, 1985, certain GI scientists, excluding Dr. Hewick, used procedures different from Miyake to purify rEPO, and then used RP-HPLC to analyze the purity. The chromatograms showed that the purified rEPO rose as a single peak. (PX 760; Tr. 13, 45). However, the fact that EPO could be partially purified without RP-HPLC does not refute the statement in the patent that it is "essential" to treat purified EPO compositions by RP-HPLC in order to obtain *homogeneous* EPO protein. (PX 500, Col. 2, 11. 49-52). Amgen has introduced no testimony that those skilled in the art would consider a 90% pure composition to be "homogeneous," and has not introduced any testimony that there is a substantial likelihood that this information would have affected the patent examiner's decision.

(j) Amgen argues that Chugai's attorney, Mr. Moroz, knew or should have known that he was mischaracterizing the *Parsons et al.* reference. However, that reference was equally available to the patent examiner.

(k) Amgen asserts that GI engaged in inequitable conduct by failing to disclose miscellaneous facts. Amgen has failed to adequately brief or document his catchall claim. As a preliminary matter, the record is devoid of any evidence that would establish deliberate knowing withholdings of any kind by Dr. Hewick or GI. Dr. Hewick was a credible witness who spoke carefully and candidly about his work. Even Amgen's own expert, John Wall, conceded that Dr. Hewick was an expert in the field of protein chemistry whose analysis he was prepared to rely on. (Tr. 37, 44). Moreover, even if Dr. Pierce's

analysis were better than Dr. Hewick's with respect to a particular assumption or conclusion, at most the differences in analysis represented disagreements between two men of ordinary, indeed extraordinary, skill in the art, not fraudulent conduct. There is no evidence that Dr. Hewick withheld any information he believed was material to the patent examiner. The court now deals with the specific facts which Amgen claims were misrepresented.

i. Amgen argues that the procedures used by Dr. Miyake and his assistant, Dr. Shimizu, to purify the shipments of EPO to GI in 1984 differed in significant ways from the procedures used in Dr. Goldwasser's laboratory in 1976.

With respect to the second shipment, Dr. Shimizu believed that the purification procedures were "slightly different" and there was "contamination with other proteins and desialylation of EPO." (PX 588, p. 47). Dr. Hewick confirmed that the sample was unrepresentative. He conducted an SDS-PAGE analysis and ran reverse phase chromatograms, and saw that the results were not only inconsistent with shipment one and "atypical," but also that the patterns were "too complex." (Tr. 15, 154-155). Dr. Hewick felt it was a "very dirty prep." (Tr. 15, 154). There were more bands spread over a wide molecular weight range on SDS gels, and there was a complex pattern of peaks and zones on the 280 and 214 absorbance traces. (Tr. 15, 154).

Therefore, Amgen has not presented clear and convincing evidence that the contamination in shipment 2 supports its argument that the differences in the purification procedures used by Miyake in 1976 and 1984 created a contaminated EPO in shipments 1, 3, and 4. Even if Amgen's analysis were correct, it has not demonstrated that Hewick made any material misrepresentations or omissions to the patent examiner.

ii. Amgen argues that GI failed to disclose material facts about the specific activity data for the uEPO in shipment three. In particular, Dr. Pierce, Amgen's expert, attacked the mean

value of 83,005 IU/AU computed by Dr. Miyake from 15 data points, since the three values which were averaged — 112,740, 87,671, and 48,604 IU/AU — were "so divergent that you cannot get meaningful information by a simple averaging." (Tr. 12, 74-75; 18, 119). Dr. Pierce also testified that only the 112,740 value fell along the range of the standard curve. (Tr. 18, 120). However, Dr. Miyake had been calculating specific activity values for EPO for at least eight years, and in fact, the average value of 83,005 IU/AU is consistent with the values reported in the *Miyake et al.* paper. Dr. Pierce's testimony does not provide clear and convincing evidence that Dr. Hewick was acting unreasonably in relying on Miyake's reputed average specific activity level.

Amgen also criticizes Dr. Hewick for not reporting that he assumed the assay was "*in vitro*" only. However, Dr. Hewick believed there was a good correspondence between the *in vitro* and *in vivo* specific activity values of uEPO. (Tr. 13, 28). This is corroborated by the fact he assumed the uEPO he put into the chromatographic column was sialated so that the *in vivo* and *in vitro* values would be the same. (Tr. 12, 34). If the uEPO were desialated, the liver would destroy the hormone and the molecule would not be able to stimulate red blood cell production. (Tr. 12, 34). Although data subsequently developed by Chugai cast doubt on this assumption, see pp. [A163-A164] *supra*, there is no clear evidence that Dr. Hewick failed to disclose information he knew to be material. Even if his assumption turned out to be incorrect, Amgen has not provided clear and convincing evidence that the *in vivo* values specifically would have been so different as to have undermined Dr. Hewick's conclusions, particularly since the *Miyake et al.* article reported a mean value of 70,400 u/mg by *in vivo* bioassay (the fasted rat method). (PX 528, pp. 5558, 5563).

iii. Although Amgen concedes that Dr. Hewick discovered some contamination in the 1984 uEPO materials received from

Dr. Miyake, it argues that Dr. Hewick could not reasonably assume that his observations with respect to the 1984 materials were equally applicable to the materials made in Dr. Goldwasser's laboratory in 1976 and published in the 1977 *Miyake et al.* paper because there were substantial differences in the procedures used by Dr. Miyake in 1984 and the 1976 procedures used in Dr. Goldwasser's laboratory. (AF 1120-1121).

Amgen points to the following differences. In 1976, Dr. Miyake used phenol treatment to deactivate the natural enzymes which attack uEPO and cause it to lose potency, but in 1984, he instead used heat treatment. This change in procedures was reported in the '195 patent. In addition, Dr. Miyake used DEAE cellulose in 1984, but DEAE agarose in 1976. However, Dr. Miyake testified changes in the heat treatment from 1976 to 1984 made no difference. (Miyake Dep. Tr. 343-44). Miyake specifically informed Dr. Hewick that the substitution of heat for the phenol treatment and DEAE cellulose for agarose made no difference in the resulting purity. (Tr. 11, 42). Miyake confirmed with Dr. Fritsch that the heat treatment substitution made no difference. (Tr. 24, 154-155).

Also, Dr. Hewick testified that he had personally used DEAE agarose and cellulose, and there are no "real functional differences" between the two techniques. (Tr. 15, 152). Dr. Pierce had no personal experience using any of these Miyake procedures on EPO or on any other glycoprotein. (Tr. 19, 150). Moreover, at a deposition in June, 1989, Dr. Pierce stated he had not reached any conclusion as to whether there was any significance to using heat treatment rather than phenol treatment, even though at trial he said he had reached a conclusion

based on his own experience with other glycoproteins and his review of the literature. (Tr. 19, 152-153). In light of his dearth of personal experience with the Miyake purification procedures on EPO and his changed testimony on the subject, Pierce's testimony is not clear and convincing evidence that the differences in procedures were material. (Tr. 19, 155-156).

Moreover, even if these differences were material, there is no indication Dr. Hewick knew this and made misrepresentations to the examiner.

Amgen also points to the fact that instead of using calcium chloride as the salt solution, Dr. Miyake substituted sodium chloride; that Miyake changed the salt concentration of the eluting buffers in the DEAE purification step; and that Dr. Miyake did not use lithium chloride in the ethanol fractionation purification step, as had been done in 1976. Dr. Pierce testified that these changes could affect the purity of the EPO composition. (Tr. 18, 78-82). However, the differences in procedures were derived from the notebooks of Dr. Miyake, and Amgen has pointed to no evidence that Dr. Hewick knew about these differences. (Tr. 18, 72-84). Therefore, there is no evidence of a misrepresentation. Moreover, Dr. Pierce did not testify about the extent to which the changes would affect the purity, and therefore his testimony does not provide clear and convincing evidence that any resulting decrease in purity was material.

iv. Amgen argues that the purification procedures which resulted in Miyake shipment 1 were spread over an inordinately long time. However, there was no expert testimony that this time span made a difference. Indeed, the chromatograms and SDS-gels on shipments 3 and 4, upon which Dr. Hewick relied, were consistent with those done on shipment 1. Therefore, there is no clear and convincing evidence that the time span was material.

v. Amgen argues that the actual data obtained from the 1976 and 1984 preparations shows they were different. (AF

1122). However, Dr. Miyake's own gels on the 1984 materials showed a single band, just as reported in the Miyake article (Tr. 24, 153-154). Dr. Hewick was using a different gel system from Dr. Miyake, and a ten-fold more sensitive staining procedure than Dr. Miyake. (Tr. 15, 74; 11, 62). Therefore, the fact that one gel system showed multiple bands and another only one band reflects a difference in the sensitivity of the gel system, not an indication that the composition of the materials was different. (Tr. 11, 62). Moreover, the 128,620 specific activity value could reasonably have been considered one data point, not a mean value, see p. [A166] *supra*, and the *ex parte* test on the June 30, 1976 material does not provide clear and convincing evidence that the 1976 material was pure. (*See* pp. [A152-A154] *supra*).

vi. Amgen argues that Dr. Hewick could not reasonably assume that all of the material under the EPO peaks of the chromatograms was EPO and that all of the material under the non-EPO peaks was not EPO. However, Dr. Hewick conducted n-terminal sequence analysis on shipments one and three which confirmed his conclusions. (Tr. 15, 110-123, 169-171). To support its position that the EPO peak included non-EPO molecules and the non-EPO peak included EPO molecules, Amgen relies on SDS-PAGE gels about which there has been no expert testimony.[16] (AF 1081-82). Therefore, there is no clear and convincing evidence that Dr. Hewick's assumptions were incorrect as to which chromatogram areas reflected EPO and which reflected non-EPO.

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[16] Amgen also argues that Dr Mufson's group at GI conducted *in vitro* bioassays on the fractions and found EPO activity from the non-EPO peaks. (AF 1094-1096). However, Dr. Mufson told Hewick that there was no significant activity in the non-EPO peaks. (Tr. 16, 52). Amgen's reliance on Jane Aghajanian's calculations in her laboratory notebook, which are incomprehensive in the absence of explanation by an expert, is not clear and convincing evidence to the contrary.

vii. Amgen further argues that Dr. Hewick could not reasonably correlate the amount of absorbance or peak area with the amount of protein present because the peaks only reflect the proportionate absorbance of ultraviolet light. (AF 1125). Dr. Pierce testified: "You cannot equate the amount of absorption under a peak with the weight or mass of material that is there." (Tr. 18, 125). Dr. Hewick testified that the trace at the wavelength of 280 gives a "relative idea of how much there is," but the comparative amounts depend on the extinction coefficient of the proteins — "some proteins may have a higher amount of tryptophan or tyrosine in them, so they will absorb more for the actual mass of protein than, say, another protein that has, say, fewer numbers of tyrosine or tryptophan." (Tr. 11, 76). However, Dr. Hewick testified that in a complicated mixture, a trace will reflect a relative amount of one protein compared to another. (Tr. 11, 76) Moreover, he testified that the fact that the tracing does not reveal the relative mass of the protein but only the relative absorbance is "irrelevant in terms of computing from those chromatograms what the specific activity of EPO is since it's described in terms of absorbance units of protein." (Tr. 11, 81). Amgen has not provided clear and convincing evidence that Dr. Hewick's testimony is wrong.

viii. Amgen argues that Dr. Hewick failed to take into account "differential hangup." Dr. Pierce testified that EPO could have been preferentially hungup on the column which would affect the chromatogram. (Tr. 19, 6-7). However, Dr. Pierce conceded that neither he nor anyone else had any data on what percentage of EPO absorbance units came through this column. (Tr. 19, 6). Dr. Hewick testified that he ran blank gradients on the reverse phase after he conducted the runs on the Miyake materials and he did not see any "ghost peaks" which would indicate differential hangup. (Tr. 21, 83-85). Moreover, he did multiple injections of the samples with differing amounts and saw a proportional increase in all parts of the chromatogram,

which indicated no differential hangup. (Tr. 21, 85). Accordingly, there is no evidence that differential hangup affected Dr. Hewick's calculation of specific activity.

ix. Amgen challenges Dr. Hewick's method of calculating specific activity by measuring the area under the peak. However, as even Dr. Strickland, Amgen's scientist, conceded, Dr. Hewick's cutting and weighing of the areas above the baseline on the chromatographs is a well-recognized technique for examining specific activity. (Tr. 15, 175-176; 14, 153-154). Dr. Goldwasser's testimony to the contrary is too ambiguous and conclusory to be persuasive. (Goldwasser Dep. Tr. Vol. II 772-774, 803). The court already has rejected Amgen's argument that Dr. Hewick improperly relied on the specific activity of 83,005 for shipment 3, and as to why he refused to rely on the 112,740 specific activity value from shipment 2. Amgen argues that Hewick should have relied on the mean *in vitro* specific activity value of 148,000 IU/AU for shipment four. However, it points to no testimony from Dr. Hewick or any expert as to whether this specific activity value casts doubt on Dr. Hewick's conclusion as to the purity of shipment 4. Moreover, this specific activity value was not generated until July, 1985, after the patent application was filed, and Dr. Hewick had never seen Miyake's reported data until his testimony at trial (Tr. 13, 9). (PX 672).

5. Enablement

Pursuant to 35 U.S.C. § 112, the patent specification "shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same."

That some experimentation may be necessary in order to practice the invention does not render an application non-enabling under § 112 so long as the amount of experimentation is

not unduly extensive. *Phillips Petroleum Co.* v. *U.S. Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1987), *aff'd* 865 F.2d 1247 (Fed. Cir. 1989). Whether an application is sufficiently enabling is to be determined as of its filing date rather than as of the date of trial. *Id.* Thus, post-filing developments in the art are irrelevant to the enablement inquiry. *Id.* The critical inquiry is whether at the time the application was filed, the application contained a description sufficient to enable one skilled in the art to practice the invention. *Id.*

Here, the claimed invention is homogeneous erythropoietin with certain characteristics. Amgen has failed to establish by clear and convincing evidence that the specification fails to enable one skilled in the art to obtain a pure EPO composition with these characteristics.

First, Amgen contends that the patent does not enable one skilled in the art to obtain uEPO meeting the claims' 160,000 IU/AA specific activity test for "homogeneous" EPO. Amgen relies primarily on specific activity data for natural EPO submitted to the FDA by Chugai and data reported by Dr. Kawakita. With respect to Dr. Kawakita's data, Amgen points out that the RP-HPLC was applied to partially purified uEPO, and an *in vivo* specific activity level of only 101,000 IU/AU was obtained. (PX 721, p. 11). Amgen stresses that the 188,000 IU/AU specific activity was derived only by using an additional step "Superose 12." However, it appears from Dr. Kawakita's table demonstrating the specific activity resulting from his purification steps, that the specific activity of the uEPO put on the RP-HPLC column was only 22,200. (PX 721, p. 11). The '195 patent teaches that a "purified" EPO composition "preferably having a specific EPO activity of at least about 50,000, preferably at least about to 80,000 IU per absorbance unit at 280 nm" should be obtained before application of RP-HPLC. (PX 500, Col. 3, 11. 7-12). The fact that Dr. Kawakita's use of RP-HPLC did not result in pure EPO is therefore not clear and convincing evidence of non-enablement.

With respect to the data submitted to the FDA which show specific activity levels below 160,000 IU/Au, Amgen has provided no evidence to indicate that those samples were prepared by the *Miyake et al.* procedures or their equivalent, and that the materials applied to the HPLC column had a specific activity of at least 50,000 IU/AU as taught by the patent. (PX 811, p. 978).

Using the procedures taught by the '195 patent, Kung, one of the co-authors of the *Miyake et al.* paper and a colleague of Dr. Goldwasser, Amgen's consultant, used RP-HPLC on uEPO prepared by the Miyake procedures and obtained homogeneous EPO; also, Dr. Goldwasser's laboratory in 1987 adopted RP-HPLC as a final step in the purification procedures for uEPO. Amgen never addressed these two strong pieces of evidence cited by GI in support of enablement.

A more troubling argument is that the '195 patent fails to enable the purification of rEPO. It is undisputed that GI tried and failed to purify rEPO using RP-HPLC, and this failed experiment is disclosed in Example 2 of the patent. Indeed, although Amgen had at one point considered using RP-HPLC to purify rEPO, it ultimately used a related, but not identical, purification technique of reverse phase hydrophobic chromatography.

From a legal point of view, a patent is valid if it enables a person of ordinary skill in the art to make the invention. Here, the '195 patent enables a person of ordinary skill in the art to obtain homogeneous EPO from natural sources. At the time of the filing of the '195 application, those of ordinary skill in the art had not yet successfully developed a method of purifying EPO from recombinant sources. The fact that different methods for obtaining homogeneous EPO by purifying rEPO were subsequently developed does not make the '195 patent specifications non-enabling. It is well-established that a state of the art coming into existence after the filing date of an application

cannot be used in determining enablement under 35 U.S.C. § 112. *In re Hogan*, 559 F.2d 595, 605 (C.C.P.A. 1977) (where an application enabled those skilled in the art in 1953 to make and use a "solid polymer" and disclosed the only way then known to make such a polymer in crystalline form, the claim was not invalid as non-enabling as to solid polymers in amorphous form which did not exist until 1962). With respect to this firm precedent against use of a later state of the art in determining enablement, there is no distinction between mechanical or electrical fields of invention where there is a high level of predictability, and fields of invention involving a lower level of predictability in chemical reactions and physiological activity. *Id.* at 606. *See also Phillips Petroleum Co.* v. *U.S. Steel Corp.*, 673 F. Supp. at 1292 ("A patent applicant is not required, however, to predict every possible variation, improvement or commercial embodiment of his invention."). *Cf. Scripps Clinic & Research Foundation* v. *Genentech, Inc.*, 666 F. Supp. at 1390-95 (where Factor VIII:C, an agent essential to blood clotting was purified from human or porcine plasma in 1982 and was subsequently manufactured through recombinant techniques in 1984, the recombinant product "having the same material structural and functional characteristics as the plasma-derived preparation," was found to be an infringement of the patent covering the natural product).

Amgen argues that the uEPO is a different product than the rEPO. It relies on the data generated by defendants that the *in vivo* specific activity of the highly purified urinary EPO appeared to be approximately 65% that of recombinant EPO because of the degradation of EPO purified from pooled urine which has been excreted through the kidney. (PX 811, p. 984; PX 812, p. 36). Amgen also points to testimony by Dr. Hewick that the use of RP-HPLC on rEPO in Example 2 of the '195 patent did not work because the level of expression of the rEPO probably was not high and the EPO was contaminated

with a "different set of . . . proteins," i.e., CHO or COS proteins, than the contaminants of uEPO. (Tr. 16, 136).

However, the overwhelming evidence, including Amgen's own admissions, establishes that uEPO and rEPO are the same product. The EPO gene used to produce rEPO is the same EPO gene as the human body uses to produce uEPO. (Tr. 25, 14). The amino acid sequences of human uEPO and rEPO are identical. (Chugai's Req. Adm. to Amgen No. 436; Egrie Dep. Tr. 2-165). There are no known differences between the secondary structure of rEPO produced in a CHO cell and EPO produced in a human kidney. (Chugai's Req. Adm. to Amgen No. 437).

Amgen's own scientists have concluded that by all criteria examined, rEPO is the "equivalent to the natural hormone." In particular, they noted that the uEPO preparation had an equivalent biological activity in the RIA and bioassays. (DX 323, pp. 217-218).

Amgen's Product License Application to the FDA states that all "physical tests performed on both r-HuEPO and u-HuEPO . . . show these proteins to be indistinguishable"; that r-HuEPO and u-HuEPO are "indistinguishable in their biological and immunological properties"; and that testing "confirms the similarity of the secondary and tertiary protein structures of r-HuEPO and u-HuEPO as predicted by the equivalence of their immunological and biological activities." (DX 328, pp. 762, 782, 789).

Further, Dr. Sadler, who directs a biochemical molecular biology research laboratory at the Howard Hughes Medical Institute at Washington University in St. Louis, testified in a deposition that rEPO is "indistinguishable" from its natural counterpart. (Sadler Dep. Tr. 31-32).

Certainly the difference between the *in vivo* specific activity of uEPO and rEPO as reported by defendants in the IND is puzzling and relevant to the equivalence of rEPO and uEPO.

However, there was no expert testimony by Amgen concerning any differences between the two products, and Amgen's own publications and documents seem to dispute any differences. Therefore, Amgen has failed to demonstrate by clear and convincing evidence a difference between the two products.

Finally, Amgen argues that the '195 patent does not enable attainment of specific activities within the upper ranges of the "open-ended" claim to specific activity values falling within the "at least 160,000" limitation, such as, for example, 190,000. Relying on *Fisher*, Amgen argues that no specific activity value in that range has been even arguably attained by defendants, yet the claim would cover any future improvement in processing that resulted in such a higher value. In *Fisher*, the court held that a claim to a hormone with a potency of at least 1 international unit of activity per milligram did not bear a "reasonable correlation to the scope of enablement provided by the specification to persons or ordinary skill in the art." 427 F.2d at 839. It ruled:

> The issue thus presented is whether an inventor who is the first to achieve a potency of greater than 1.0 for certain types of compositions, which potency was long desired because of its beneficial effect on humans, should be allowed to dominate *all* such compositions having potencies greater than 1.0, including future compositions having potencies far in excess of those obtainable from his teachings plus ordinary skill.
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> ****
>
> Our conclusion is in no way opposed to the principles of the cases cited by appellant in support of his contention that he is entitled to coverage of the breadth now sought. [Those cases] each involved claims to substantially pure compositions. Such

> claims do not present the same breadth problem as here, because in those cases the possible range of further purification was either small or nonexistent. Such claims have an inherent upper limit of 100% purity, whereas in the present case it would appear theoretically possible to achieve potencies far greater than those obtained by appellant.

Id. at 839-840.

Here, the claim is to a homogeneous preparation of EPO. Amgen has not provided clear and convincing evidence that a composition with the characteristics outlined in claim 1 is not substantially pure, or that other compositions have substantially higher specific activity characteristics.

B. Infringement.

On February 24, 1988, Judge Young granted a motion for partial summary judgment that recombinant EPO infringes claims 1, 3, 4 and 6 of the '195 patent.[17] To the extent Amgen wants to raise the issue of "reverse doctrine of equivalents," it should request reconsideration by Judge Young.

With respect to claims 2 and 5, defendants do not assert infringement, and judgment declaring noninfringement will be entered on behalf of Amgen on those claims. *Environmental Instr., Inc.* v. *Sutron Corp.*, 877 F.2d 1561, 1566 (Fed. Cir. 1989) (where a patent owner decided not to pursue a claim of infringement on the eve of trial, but did not move to dismiss the claim, the claim of infringement remained in the case).

C. Willfulness

In determining whether an infringer acted in bad faith as to merit an increase in damages awarded against him, the court will

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[17] The court has found that claim 4 and claim 6, which incorporates claim 4 by reference, are invalid as indefinite. (*See* p. [A170] *supra*). Therefore, Amgen will not be held liable for infringement of those claims.

consider the totality of the circumstances, including (1) whether the infringer deliberately copied the ideas or design or another; (2) whether the infringer, when he knew of the other's patent protection, investigated the scope of the patent and formed a good-faith belief that it was valid or that it was not infringed, and (3) the infringer's behavior as a party to the litigation. *Bott* v. *Four Star Corp.*, 807 F.2d 1567, 1572 (Fed. Cir. 1986).

When a potential infringer has actual notice of another's patent rights, he has the duty to "exercise due care to determine whether or not he is infringing." *Id.* This usually includes the duty to seek and obtain competent legal advice before engaging in activity that may result in infringement. *Id.*

Amgen presents the following evidence to demonstrate lack of willful infringement. The '195 patent issued on June 30, 1987. By August 28, 1987, Amgen had received a "strongly held" opinion from the Allegretti firm that the '195 patent was not infringed by Amgen. (PX 866). On October 22, 1987, this non-infringement opinion was independently confirmed by the Marshall, O'Toole firm. (PX 864). In October, 1987, Amgen received two written opinions from these two firms that the '195 patent was invalid.

Although Dr. Rathmann, a founding officer of Amgen and its chief executive officer until 1988, could not recall reading or seeing an opinion of outside counsel, in-house counsel, Robert Weist, communicated these opinions orally to Dr. Rathmann. (Rathmann Dep. Tr. 241-248).

Following Judge Young's entry of partial summary judgment of infringement on February 24, 1988, Amgen sought and received a 72-page written opinion from a New York firm, Pennie & Edmonds, dated May 2, 1988, that the '195 patent was invalid and unenforceable. (PX 868).

Defendants argue willfulness because Amgen did not obtain any opinions of outside counsel concerning the '195 opinion after Judge Young issued his written opinion dated January

31, 1989 detailing the basis for his ruling that Amgen had infringed the '195 patent, and continued to manufacture recombinant EPO after that date. However, defendants do not point out how the written opinion differed from the oral entry of partial summary judgement on February 24, 1988 so that a new opinion of counsel was required.

Defendants obtained three different opinions on the invalidity of the '195 patent, which were written in great detail. The court finds no evidence of bad faith which would justify a finding of willful infringement.

IX. CONCLUSION

For the reasons stated herein, the court finds that:

1) Claims 2, 4 and 6 in the '008 patent are valid;

2) Claims 7, 8, 23-27 and 29 in the '008 patent are invalid;

3) GI has infringed claims 2, 4-8, 23-25, 27 and 29 in the '008 patent;

4) Chugai has not infringed the '008 patent;

5) Claims 1 and 3 in the '195 patent are valid.

6) Claims 4 and 6 in the '195 patent are invalid.

7) Amgen has infringed claims 1, 3, 4 and 6 in the '195 patent.

8) Amgen has not infringed claims 2 and 5 in the '195 patent.

9) This is not an "exceptional" case under 35 U.S.C. § 285 warranting an award of attorneys fees, costs and expenses to any party.

PATTI B. SARIS
United States Magistrate
12/11/89 1:40 p.m.

APPENDIX C

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN, INC.,
Plaintiff,

v. CIVIL ACTION NO. 87-2617-Y

CHUGAI PHARMACEUTICAL CO., LTD.,
AND GENETICS INSTITUTE, INC.,
Defendants.

MEMORANDUM AND ORDER

YOUNG, D.J. January 31, 1989

This action involves the alleged infringement of several patents covering erythropoietin, a protein which circulates in the blood and stimulates the production of red blood cells. Erythropoietin is used primarily for the clinical treatment of anemia, particularly anemia caused by renal disease.

In essence, this case is a battle over turf. The plaintiff Amgen, Inc. ("Amgen") owns a patent, the claims of which include purified and isolated DNA sequences encoding erythropoietin as well as host cells transformed or transfected with a DNA sequence. The defendant Genetics Institute, Inc. ("Genetics") owns, and the defendant Chugai Pharmaceutical Co., Ltd. ("Chugai") licenses, a patent which involves compositions comprised of highly purified erythropoietin. Although the contested property rights may revolve about fundamental scientific principles, the issues raised here rattle, ostensibly at

least, the traditional foundations of patent law; that is, how do putative proprietary interests in recombinant technology interact with traditional concepts of patent law?

This matter is presently before the Court on the motions of Chugai and Genetics for summary judgment pursuant to Fed. R. Civ. P. 56 on various claims asserted by the parties.

I. FACTUAL BACKGROUND

Erythropoiesis, which is the production of red blood cells, occurs continuously throughout the human life span in order to offset cell destruction. This process enables a sufficient number of red blood cells to be available for proper tissue oxygenation, but not so many that such cells would impede blood circulation. Red blood cells are formed in the bone marrow, and this formation is stimulated by erythropoietin, a circulating glycoprotein.

The life of human red blood cells is about 120 days. Thus, about 1/120 of the total red blood cells are destroyed daily in the reticuloendothelial system.[1] Concurrently, a relatively equal number of red blood cells are produced daily to maintain the level of such cells. Red blood cells are produced by the maturation and differentiation of erythroblasts[2] in the bone marrow; erythropoietin is the factor which acts on less differentiated cells and induces their differentiation to red blood cells.

Because erythropoietin is a stimulating factor in the production of red blood cells, it is a promising therapeutic agent in the treatment of those blood disorders characterized by low or de-

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[1] The reticuloendothelial system "function[s] in elimination of worn out cells, esp[ecially] red blood cells; in repair of injured tissue; and in defense mechanisms, both local and general, of the body." *Taber's Cyclopedic Medical Dictionary* 1481 (C. Thomas ed. 15th ed. 1985).

[2] An erythroblast is "[a] young or immature red blood cell, i.e., the precursor of an erythrocyte, the normal, mature red blood cell." 2 J. Schmidt, *Attorney's Dictionary of Medicine* E-128 (1988).

fective red blood cell production such as anemia and, in particular, renal anemia. The use of erythropoietin, however, is not common in practical therapy at the present time because it is not yet widely available.

The preparation of erythropoietin products generally has been accomplished through the concentration and purification or urine from both healthy patients and those exhibiting high erythropoietin levels, such as those patients suffering from aplastic anemia. Erythropoietin also can be recovered from sheep blood plasma; however, such erythropoietin is expected to be antigenic in humans. Another technique for producing erythropoietin is recombinant technology in which erythropoietin is produced from cell cultures into which genetically engineered vectors containing the erythropoietin gene have been introduced. Regardless of the source, however, the erythropoietin protein must be purified to homogeneity in order to use it therapeutically.

It had been thought in the scientific community that erythropoietin purified by methods described by Miyake[3] was homogeneous as measured by a specific activity on the order of 80,000 International Units (IU) per absorbance unit (AU) at 280 nanometers (A280) (hereinafter, "IU/AU"). Dr. Rodney Hewick ("Dr. Hewick"), however, discovered that truly homogeneous erythropoietin has a specific activity of at least about 160,000 IU/AU and, further, that Miyake's erythropoietin composition is not in fact homogeneous, but contains large

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[3]The method of Miyake, which was described by Miyake, et al. in 252 *J. Biol. Chem.* 5558 (1977), involves deactivating any proteolytic enzymes by preparing crude erythropoietin preparations with pheno p-aminosalicylate. The method of Miyake includes the following steps: ethanol precipitation, DEAE-agarose fractionation, sulfopropyl-Sephadex chromatography, gel filtration, and hydroxylapatite chromatography. *See* United States Patent No. 4,677,195 at cols. 2-3 (Declaration of Rodney M. Hewick in Support of Defendants' Motion for Summary Judgment of Patent Infringement [hereinafter, "Hewick Decl."], Exhibit A).

amounts of several non-erythropoietin protein contaminants. Dr. Hewick was subsequently successful in producing homogeneous erythropoietin.

On June 30, 1987, the United States Patent and Trademark Office ("the Patent and Trademark Office") awarded Dr. Hewick United States Patent No. 4,677,195 entitled "Method for the Purification of Erythropoietin and Erythropoietin Compositions" ("the '195 patent")[4] covering both a nonrecombinant method for purifying erythropoietin and compositions of highly purified erythropoietin. Dr. Hewick assigned the '195 patent to Genetics, a Delaware corporation having a principal place of business in Cambridge, Massachusetts. Genetics then licensed the rights of the '195 patent to Chugai, a Japanese corporation having a principal place of business in Tokyo, Japan.

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[4]The relevant claims of the '195 patent, those which are allegedly infringed by Amgen, are the following:

> 1. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers.
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> . . .
>
> 3. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 1 in a pharmaceutically acceptable vehicle.
>
> 4. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least about 160,000 IU per absorbance unit at 280 nanometers.
>
> 6. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 4 in a pharmaceutically [sic] acceptable vehicle.

United States Patent No. 4,677,195 at cols. 8-10 (Hewick Decl., Exhibit B).

The plaintiff Amgen is a Delaware corporation having a principal place of business in Thousand Oaks, California, and is engaged in the development and the eventual commercialization of recombinant erythropoietin for human pharmaceutical applications. A division of Amgen, Amgen Biologicals, has manufactured and sold erythropoietin produced by recombinant DNA techniques since June 30, 1987, the date on which the '195 patent was issued. Chugai and Genetics assert that this recombinant erythropoietin[5] infringes the claims of the '195 patent.

The other principal patent in this litigation is United States Patent No. 4,703,008 entitled "DNA Sequences Encoding Erythropoietin" ("the '008 patent"). On October 27, 1987, the Patent and Trademark Office issued the '008 patent to the inventor Fu-Kuen Lin, who assigned it to Kirin-Amgen, Inc. ("Kirin-Amgen"), a California corporation owned equally by Amgen and Kirin Brewery ("Kirin"). Kirin-Amgen was created under a joint venture agreement between Amgen and Kirin for the purpose of the further development and eventual commercialization of recombinant erythropoietin for human pharmaceutical applications. The '008 patent "relates generally to the manipulation of genetic materials and, more particularly, to recombinant procedures making possible the production of

[5] The Amgen erythropoietin has the following characteristics: 1) "The specific activity of Amgen Biologicals' ultrapure erythropoietin is 160,000 units/A280 as determined by the *in vivo* exhypoxic polycythemic mouse bioassay . . . ," Amgen Biologicals, *Untitled Document on Human Recombinant Erythropoietin* (hereinafter, "Amgen Biologicals") at 1 (unnumbered) (December 1985) (footnote omitted) (Hewick Decl., Exhibit C); 2) "Ultrapure erythropoietin is a homogeneous preparation that yields a single band and peak when analyzed by SDS polyacrylamide gel electrophoresis and HPLC respectively," *id.* at 3 (unnumbered); 3) The average molecular weight of the recombinant erythropoietin on SDS-PAGE is 34,700 daltons, Declaration of Michael A. Recny in Support of Defendants' Motion for Summary Judgment of Patent Infringement at para. 7 (hereinafter, "Recny Decl."). Amgen also states in its own product literature that "[analysis] demonstrates biological and immunological equivalence between Amgen Biologicals' recombinant erythropoietin and material derived from human urine." Amgen Biologicals at 1 (unnumbered).

polypeptides possessing part or all of the primary structural conformation and/or one or more of the biological properties of naturally-occurring erythropoietin." United States Patent No. 4,703,008 at col. 1 (Complaint, Exhibit A). The claims of the '008 patent include numerous purified and isolated DNA sequences encoding erythropoietin in addition to host cells transformed or transfected with a DNA sequence. *See id.* at cols. 39-42.

On October 27, 1987, the same day that the '008 patent was issued, Amgen filed this action against Chugai and Genetics, alleging that 1) the defendants' production, use and sale of recombinant erythropoietin infringe the '008 patent; 2) the '195 patent is invalid, or, in the alternative, Amgen does not infringe the claims of the '195 patent, and; 3) the defendants' future activities vis a vis the production and sale of recombinant erythropoietin will infringe the '008 patent.

Thereafter, Amgen filed a complaint with the International Trade Commission ("the Commission") on January 4, 1988, alleging that Chugai's importation of recombinant erythropoietin, which is manufactured in Japan using genetically engineered host cells, violates Section 337 of the Tariff Act of 1930 (19 U.S.C. sec. 1337) and 19 U.S.C. sec. 1337a.* Chugai filed a motion for summary determination seeking to terminate

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* Specifically, Amgen asserted in the complaint filed with the Commission:

> Chugai imports into the United States recombinant erythropoietin manufactured in Japan by a process utilizing genetically engineered host cells containing DNA sequences coding for human erythropoietin. Utilization of such genetically engineered host cells constitutes infringement of the '008 patent claims. Chugai, therefore, is engaged in the importation of a product produced by a process covered by the claims of the '008 patent in violation of 19 U.S.C. sec. 1337a. . . .

United States International Trade Commission Complaint Exhibit 22 at 1 (Exhibit B to the Memorandum in Support of Defendant Chugai Pharmaceutical Co., Ltd's Motion for Summary Judgment [hereinafter, "Chugai Memorandum II"]).

the Commission's investigation. The Administrative Law Judge, however, denied the motion on March 7, 1988.

Chugai and Genetics answered and counterclaimed in the present action, alleging that 1) Amgen has infringed the '195 patent; 2) the '008 patent does not provide patent protection for recombinant erythropoietin; 3) the filing of a complaint by Amgen with the Commission constitutes unfair competition; 4) the '008 patent is invalid; and 5) Amgen's utilization of the '008 patent constitutes a violation of Section 2 of the Sherman Act. Chugai and Genetics then filed a motion for partial summary judgment on the claim that Amgen infringes the claims of the '195 patent. On February 24, 1988, the Court heard oral argument and then granted the motion. Chugai filed a motion for summary judgment on May 12, 1988, and, after oral argument of June 24, 1988, the Court took the Motion under advisement.

The Court will here treat the following matters:

(1) the motion of Chugai and Genetics for partial summary judgment — heard and decided on February 24, 1988 — on the issue whether Amgen's product infringes the '195 patent; i.e., the Court will set forth the reasoning underlying its February 24 ruling;

(2) the motion of Chugai for summary judgment seeking a determination that '008 patent is unenforceable due to Amgen's alleged acts of patent misuse or, in the alternative, that the '008 patent contains no process claims, and thus does not cover Chugai's process of manufacturing recombinant erythropoietin.

II. DISCUSSION

Under Fed. R. Civ. P. 56, summary judgment is appropriate if "there is no genuine issue as to any material fact and . . . the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56(c). Since one principal purpose of summary

judgment "is to isolate and dispose of factually unsupported claims or defenses," *Celotex Corp.* v. *Catrett*, 477 U.S. 317, 323-24, 106 S. Ct. 2548 (1986), it is now well established that Fed. R. Civ. P. 56(e)[7] "requires the nonmoving party to go beyond the pleadings and by her own affidavits, or by the 'depositions, answers to interrogatories, and admissions on file,' designate 'specific facts showing that there is a genuine issue for trial.'" 477 U.S. at 324 (quoting Fed. R. Civ. P. 56[c], [e]); *see also Anderson* v. *Liberty Lobby, Inc.*, 477 U.S. 242, 250, 106 S. Ct. 2505, (1986); *Paterson-Leitch Co.* v. *Massachusetts Municipal Wholesale Elec. Co.*, 840 F.2d 985, 992 (1st Cir. 1988).

Moreover, summary judgment is as appropriate in a patent case as in any other case where no genuine issue of fact exists and the movant is entitled to judgment as matter of law. *Moeller* v. *Ionetics, Inc.*, 794 F.2d 653, 656 (Fed. Cir. 1986); *SRI Int'l* v. *Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1116 (Fed. Cir. 1985) (en banc) (plurality opinion). Addressing the propriety of summary judgment in patent cases, the Federal Circuit has stated:

> Many, if not most, suits for patent infringement give rise to numerous and complex fact issues, rendering those suits inappropriate for summary disposition. Where no issue of material fact is present, however,

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[7] Section 56(e) provides, in pertinent part:

> When a motion for summary judgment is made and supported as provided in this rule, an adverse party may not rest upon the mere allegations or denials of the adverse party's pleading, but the adverse party's response, by affidavits or as otherwise provided in this rule, must set forth specific facts showing that there is a genuine issue for trial. If the adverse party does not so respond, summary judgment, if appropriate, shall be entered against the adverse party.

Fed. R. Civ. P. 56(e) (1988).

> courts should not hesitate to avoid an unnecessary trial by proceeding under Fed. R. Civ. P. 56 without regard to the particular type of suit involved.

Chore-Time Equip., Inc. v. *Cumberland Corp.*, 713 F.2d 774, 778-79 (Fed. Cir. 1983). In this vein, the complexity of the law and the arcane nature of the facts do not dictate whether a party survives a motion for summary judgment in a patent case. Rather, where no genuine issue of material fact exists and the moving party is entitled to judgment as matter of law, the courts properly grant summary judgment to avoid long, complex, and expensive trials which are, in fact, unnecessary.

A. Infringement of the '195 Patent.

On February 24, 1988, this Court granted the motion of Chugai and Genetics for partial summary judgment on the claim that Amgen's manufacture, use and sale of homogeneous recombinant erythropoietin infringe claims 1, 3, 4 and 6 of the '195 patent. This opinion sets forth the Court's reasoning.

The property rights conferred by a patent grant include the right to exclude others from making, using or selling the patented invention in the United States, 35 U.S.C. sec. 154;[8] *see also Zenith Radio Corp.* v. *Hazeltine Research, Inc.*, 395 U.S. 100, 135, 89 S. Ct. 1562 (1969). Such exclusive rights of the inventor are protected by 35 U.S.C. sec. 271(a),[9] which

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[8] Section 154 provides, in pertinent part:

> Every patent shall contain a short title of the invention and a grant to the patentee, his heirs or assigns, for the term of seventeen years, . . . of the right to exclude others from making, using, or selling the invention throughout the United States, referring to the specification for the particulars thereof.

35 U.S.C.A. sec. 154 (West 1984).

[9] Section 271(a) provides, in pertinent part:

> [W]hoever without authority makes, uses or sells any patented invention, within the United States during the term of the patent therefor, infringes the patent.

35 U.S.C.A. sec. 271(a) (West 1984).

forbids others from trespassing upon the inventor's patent property. This trespass of another's patent property, otherwise known as "infringement of the patent," is the foundation of patent law.

Determining whether a certain patent has been infringed requires two steps: "first, the scope of the claims must be ascertained, and then the trier must decide whether the claims cover the accused devise." *Palumbo* v. *Don-Joy Co.*, 762 F.2d 969, 974 (Fed. Cir. 1985). In other words, the initial inquiry is to delineate the boundaries of the patented invention, determining the limits of the patent claims as one who has brought an action for trespass must establish the boundaries of her real property.[10]

1. Interpretation of the Claims of the '195 Patent.

Any determination of the bounds of the patentee's rights begins with the words of the claims. The Supreme Court in *Graver Tank & Mfg. Co.* v. *Linde Air Prods. Co.*, 339 U.S. 605, 70 S. Ct. 854 (1950) stated, "In determining whether an accused device or composition infringes a valid patent, resort must be had in the first instance to the words of the claim." *Id.* at 607; *see Palumbo* 762 F.2d. at 974; *McGill Inc.* v. *John Zink Co.*, 736 F.2d 666, 672-73, (Fed. Cir.), *cert. denied*, 469 U.S. 1037 (1984). Thus, a patent is:

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[10] Addressing this inquiry of determining the scope of the patent, the Supreme Court has stated:

> The scope of every patent is limited to the invention described in the claims contained in it, read in the light of the specification. These so mark where the progress claimed by the patent begins and where it ends that they have been aptly likened to the description in a deed, which sets the bounds to the grant which it contains. It is to the claims of every patent, therefore, that we must turn when we are seeking to determine what the invention is, the exclusive use of which is given to the inventor by the grant provided for by the statute, — 'He can claim nothing beyond them.'

Motion Picture Patents Co. v. *Universal Film Mfg. Co.*, 243 U.S. 502, 510, 37 S. Ct. 416 (1917).

> "a written contract between [an] inventor and the government. . . . The consideration given on the part of the inventor to the government is the disclosure of his invention. . . . The consideration on the part of the government given to the patentee for [such] disclosure is a monopoly for seventeen years of the invention [disclosed to] the extent of the claims allowed in the patent."

Marcyan v. *Nissen Corp.*, 578 F. Supp. 485, 498 (N.D. Ind. 1982) (quoting *Krupp A.G.* v. *Midvale Steel Co.*, 191 F. 588 [, 594 (3d Cir. 1911)]) (bracketed material restores original language of *Krupp A.G.* quotation), *aff'd sub nom. Marcyan* v. *Marcy Gymnasium Equip. Co.*, 725 F.2d 687 (7th Cir. 1983). Therefore, the interpretation of patent claims is conducted according to the same general rules of construction as other contracts. *See Goodyear Dental Vulcanite Co.* v. *Davis*, 102 U.S. 222, 227, 26 L.Ed. 149 (1880).

First, if the language of the patent claim is clear, unambiguous, and undisputed, the claim is interpreted according to the words of the claim without requiring any reference to extrinsic evidence. *See Palumbo*, 762 F.2d at 974; *McGill*, 736 F. 2d at 673 n.5. If, however, the language of the claims is disputed, the court may consider a host of factors in construing such claims. *McGill*, 736 F.2d at 673; *see also Fromson* v. *Advance Offset Plate, Inc.*, 720 F.2d 1565, 1569-71 (Fed. Cir. 1983). These factors include the prosecution history of the patent, the patent specification, the other claims in the patent, and the prior art. *See SRI Int'l*, 775 F.2d at 1118 (plurality opinion); *McGill*, 736 F.2d at 673-75. These questions of patent construction are questions of law for the courts, not questions of fact for the jury. *Devex Corp.* v. *General Motors Corp.*, 667 F.2d 347, 357 (3d Cir. 1981), *aff'd*, 461 U.S. 648 (1983); *Studiengesellschaft Kohle* v. *Eastman Kodak Co.*, 616 F.2d 1315, 1324 (5th Cir.), *cert. denied*, 449 U.S. 1015 (1980).

In the instant case, the literal scope of the relevant claims of the '195 patent as described therein has not been disputed by the parties. The words of those claims are as follows:

> 1. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers.
>
> . . .
>
> 3. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 1 in a pharmaceutically acceptable vehicle.
>
> 4. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers.
>
> . . .
>
> 6. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 4 in a pharmaceutically [sic] acceptable vehicle.

United States Patent No. 4,677,195 at cols. 8-10 (Hewick Decl., Exhibit A). The erythropoietin composition covered by the '195 patent claims may therefore be broken down into essentially four characteristics: 1) homogeneous; 2) molecular weight of about 34,000 daltons on SDS PAGE; 3) movement as a single peak on reverse phase high performance liquid chromatography, and; 4) a specific activity of at least about 160,000 IU absorbance unit at 280 nanometers.

2. Infringement of the '195 Patent by the Amgen Product.

Once the scope of the patent is defined, the second inquiry focuses on determining whether the accused matter falls within the limits of the patent claims as properly interpreted. *E.g.*, *Palumbo*, 762 F.2d at 974; *Envirotech Corp.* v. *Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984). Because this second question, a comparison of the accused matter to the claims of the patent, is a question of fact, *see Palumbo*, 762 F.2d at 974; *Envirotech*, 730 F.2d at 758, a motion for summary judgment on this issue should be approached with great care, *Palumbo*, 762 F.2d at 974.

Granting summary judgment on this issue, however, is not precluded merely by the necessity of an onerous factual comparison between the patent claims and the accused device. Where the patentee demonstrates that the accused device embodies every element of the patent claim, literal infringement is established. *Stewart-Warner Corp.* v. *City of Pontiac*, 767 F.2d 1563, 1570 (11th Cir. 1985); *Builders Concrete, Inc.* v. *Bremerton Concrete Prods. Co.*, 757 F.2d 255, 257 (Fed. Cir. 1985). In the case where literal infringement is indeed established, the case ends; a trial on the issue of infringement is not then necessary.[11]

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[11] If these requirements of literal infringement are not satisfied, however, the infringement analysis does not end there. That is, even if the accused device does not fall within the literal reading of the patent claims, the test of equivalence — whether the accused device "performs substantially the same function in substantially the same way to obtain the same result," *Graver Tank & Mfg. Co.* v. *Linde Air Prods. Co.*, 339 U.S. 605, 608, 70 S. Ct. 854 (1950) (quoting *Sanitary Refrigerator Co.* v. *Winters*, 280 U.S. 30, 42, 50 S. Ct. 9 [1929]) — is a crucial question concerning infringement. Otherwise, "[t]o allow literality alone to satisfy the infringement test would force patent law to reward literary skill and not the inventor's creativity. Since the law is intended to benefit the inventor's genius and not the scrivener's talent, the structures must do the same work in substantially the same way and accomplish substantially the same result." 6 E. Lipscomb, *Walker on Patents* sec. 22:23, at 513 (3d ed. 1987) (footnote omitted). In *Graver Tank*, the Supreme Court explained that "to permit imitation of a patented invention which does not copy every

In the present case, this Court must determine whether the Amgen recombinant erythropoietin, broken down into the relevant characteristics of the erythropoietin composition covered by the '195 patent, infringes the claims of the '195 patent. As a preliminary matter, Amgen does not dispute that its recombinant erythropoietin is a homogeneous preparation.[12] In opposing the motion for partial summary judgment, Amgen argued that its recombinant product has an apparent molecular weight of about 32,000 to 38,000 daltons on SDS PAGE, and therefore does not fall within the scope of the '195 patent claim. *See* Amgen's Opposition to Chugai/GI's Motion for Summary Judgment at 12 (hereinafter, "Opposition Memorandum I").

The Court does not agree. Dr. Michael A. Recny ("Dr. Recny"), the head of the Structural Protein Chemistry Laboratory at Genetics, examined a sample of the Amgen recombinant erythropoietin and determined that the Amgen product has a molecular weight of a range of 33,000 - 36,400 daltons on SDS-PAGE, or an average molecular weight of 34,700 daltons. Recny Decl. at paras. 1, 7. He further stated that such molecular weight falls within the scope of the erythropoietin composition

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literal detail would be to convert the protection of the patent grant into a hollow and useless thing." *Id.* at 607. The Supreme Court continued:

> Equivalence, in the patent law, is not the prisoner of a formula and is not an absolute to be considered in a vacuum. It does not require complete identity for every purpose and in every respect. . . . Consideration must be given to the purpose for which an ingredient is used in a patent, the qualities it has when combined with the other ingredients, and the function which it is intended to perform. An important factor is whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was.

Id. at 609. A finding of equivalence, therefore, is a determination of fact. *E.g., id.* at 609; *Omark Indus.* v. *Textron, Inc.*, 688 F.2d 1242, 1250 (9th Cir. 1982).

[12] Amgen, in its own product specification, states, "Ultrapure erythropoietin is a homogeneous preparation. . . . " Amgen Biologicals at 3 (unnumbered) (Hewick Decl., Exhibit C).

covered by the '195 patent which is characterized by a molecular weight of about 34,000 daltons on SDS-PAGE. *Id.* Furthermore, in an article describing the human erythropoietin gene, certain Amgen scientists assert that the molecular weight of the recombinant erythropoietin is 34,000.[13] *See* Sadler Decl. at para. 14.

Presented with these asserted facts, this Court ruled that there was no genuine issue of material fact vis a vis the molecular weight of the recombinant erythropoietin. Even if the Court were to accept Amgen's argument that the recombinant erythropoietin has a molecular weight of about 32,000 to about 38,000 daltons,[14] Amgen failed to demonstrate that this variance is significant enough even to constitute a genuine issue of material fact. Without adequate factual support of its arguments, Amgen cannot succeed.

Amgen next argued that "[t]here is no definition of 'single peak by reverse phase high performance liquid chromatography (HPLC)' derivable from the '195 patent" and "Amgen's product does not meet the definition of 'single peak' by reverse phase HPLC as that term is used in the '195 patent." Opposition Mem-

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[13] This article, Lin, et al., *Cloning and Expression of the Human Erythropoietin Gene*, 82 Proc. Nat'l. Acad. Sci. USA 7580 (1985) (attached as Exhibit F to the Declaration of J. Evan Sadler in Support of Defendants' Motion for Summary Judgment of Patent Infringement [hereinafter, "Sadler Decl."]) is written, in part, by several Amgen scientists. The article states, "[The recombinant erythropoietin] has an apparent [molecular weight] of 34,000 when analyzed in an electrophoretic transfer blot." *Id.* at 7582.

[14] Of course, it is well established that the nonmoving party must go beyond the pleadings, and by affidavits, depositions, answers to interrogatories, and admissions on file, must designate specific facts showing that there is a genuine issue. *See supra* at 9-10. This, Amgen has failed to do. Instead, Amgen has merely asserted these facts in its memorandum and attached to its memorandum a technical article about recombinant erythropoietin that fails to support specifically these assertions. Such arguments, without the detailed factual support required by Rule 56, are wholly inadequate. *See Transurface Carriers, Inc. v. Ford Motor Co.*, 738 F.2d 42, 46 (1st Cir. 1984) (holding that "[m]ere assertions of counsel made in a legal memorandum are insufficient to establish the existence of a genuine issue of material fact").

orandum I at 10-11. These arguments, however, besides appearing to be inconsistent with each other, also seem inconsistent with the product specifications of the recombinant erythropoietin in the Amgen literature, which states the Amgen recombinant erythropoietin is a "homogeneous preparation that yields a single band and peak when analyzed by SDS polyacrylamide gel electrophoresis and HPLC respectively." Amgen Biologicals at 3 (unnumbered) (Hewick Decl., Exhibit C). Similarly, certain Amgen scientists state in other literature that the human recombinant erythropoietin "elutes as a single peak in HPLC gel filtration and reverse phase HPLC." Parker, et al., *Structural Characterization of Recombinant DNA-Derived Human Erythropoietin*, 45 Fed'n Proc. 1721 (Abstracts of the 76th Annual Meeting of the American Society of Biological Chemists 1986) (Sadler Decl., Exhibit E). Furthermore, in Dr. Recny's analysis of the Amgen recombinant erythropoietin, the Amgen product "eluted as a single peak at approximately 31.5 minutes which corresponds to approximately 51.5% solvent B in the gradient program. When the chromatograph obtained from the Amgen human EPO was compared to the homogeneous EPO disclosed in the '195 Patent, both compounds show movement as a single peak at substantially similar positions on the chromatographic scale." Recny Decl. at para. 7. Responding to the Recny analysis, Amgen contends that Dr. Recny's "carefully chose, but not yet cross-examined, statement" does not "show the HPLC peak by way of an exhibit so that Recny's analysis of 'single peak' can be compared to Hewick's analysis of single peak. . . ." Opposition Memorandum I at 11.

The Court is not persuaded by this argument. Both Amgen and the defendants have described their own erythropoietin as yielding or eluting a single peak in reverse phase HPLC. Further, the defendants, through Dr. Recny's analysis of the two erythropoietin substances, have produced evidence that,

with respect to a single peak in reverse phase HPLC, both substances are "substantially similar." Amgen, in response, fails "to go beyond the pleadings and by [its] own affidavits, or by the 'deposition, answers to interrogatories, and admissions on file,' designate 'specific facts showing that there is a genuine issue for trial.'" *Celotex*, 477 U.S. at 324. Amgen may not simply rely upon the promise of evidence to be developed by the cross-examination of Dr. Recny at trial. *See Manego* v. *Orleans Bd. of Trade*, 598 F. Supp. 231, 239 (D. Mass. 1984), *aff'd*, 773 F.2d 1 (1st Cir. 1985), *cert. denied*, 475 U.S. 1084 (1986). Thus, having failed to support is argument with factual development, Amgen cannot succeed on this issue.

Amgen next contended that the specific activity of the Amgen recombinant erythropoietin does not fall within the '195 patent specification of at least about 160,000 IU per absorbance unit at 280 nanometers, and thus the Amgen product does not infringe the claims of the '195 patent. Again, this Court disagrees. In its own product literature, Amgen states, "The specific activity of Amgen Biologicals' ultra-pure erythropoietin is 160,000 units/A280 as determined by the *in vivo* exhypoxic polycythemic mouse bioassay." Amgen Biologicals at 1 (unnumbered) (footnote omitted) (Hewick Decl., Exhibit C). Moreover, according to an article written by Amgen and Amgen-funded scientists, the recombinant human erythropoietin being used in clinical trials has a specific activity of 129,000 units per milligram of hormone. *See* Eschbach, et al., *Correction of the Anemia of End-Stage Renal Disease with Recombinant Human Erythropoietin*, 316 N. Eng. J. Med. 73, 74 (1987) (Recny Decl., Exhibit D). After converting this figure of 129,000 units/mg of hormone to those standards used in the '195 patent, the specific activity of the recombinant erythropoietin is about 174,000 IU per absorbance unit at 280 nanometers. *See* Recny Decl. at para. 9.

Additionally, the technical data sheet accompanying the Amgen recombinant human erythropoietin states the specific activity as greater than "160,000 units/A280 [by *in vivo* assay]." *See* Amgen Technical Data Sheet - Recombinant Human Erythropoietin at 1 (footnote omitted) (Recny Decl., Exhibit C). In short, Amgen failed to address the admissions found in its own product literature; instead, it presented this Court with other data concerning the specific activity of the re-combinant human erythropoietin, and argued that such data does not fall within the scope of the '195 patent claims. *See* Opposition Memorandum I at 9. Amgen's failure, however, to explain both the origin of this other data, and the reasons why this particular data is different from the data in other Amgen literature is fatal.[15] Simply put, Amgen has failed to raise a "genuine issue" on this point.

3. The Scope of the '195 Patent and Recombinant Technology.

Finally, a fundamental principle of patent law is that a product patent claim covers only the product itself, not the method or process for making the product. *See United States* v. *Studiengesellschaft Kohle*, 670 F. 2d 1122, 1127 (D.C. Cir. 1981).

> The essential difference between the two [types of patents, process and product,] relates to scope. A product patent gives the patentee the right to restrict the use and sale of the product regardless of how

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[15] The document containing this data is entitled "Specification: Purified Bulk-Erythropoietin" and appears to be an Amgen form. Opposition Memorandum I, Exhibit D, at 1. It bears an effective date of January 26, 1988. Amgen terms this document a "product specification." Opposition Memorandum I at 9. Nowhere does Amgen explain what this document is, what its present status is (e.g., has it since been withdrawn or revised by Amgen?), or why the specific activity figure cited in it conflicts with other Amgen data.

> and by whom it was manufactured. A process patentee's power extends only to those products made by the patented process.

Id. at 1127 (citations omitted). It is well established that if the "patent is upon a product, and if the product complained of is the patented article substantially as described, *it makes no difference by what path or process, new or old, inferior or improved, the infringing product is manufactured.*" *G.D. Searle & Co.* v. *Byron Chem. Co.*, 223 F. Supp. 172, 174 (E.D.N.Y. 1963) (quoting *Proctor & Gamble Co.* v. *Berlin Mills Co.*, 256 F. 23 [2d Cir. 1919], *rev'd on another ground*, 254 U.S. 156 [1920]) (emphasis added) (citation omitted); *Stratoflex, Inc.* v. *Aeroquip Corp.*, 713 F.2d 1530, 1541 (Fed. Cir. 1983) (stating that "[t]he determination of non-infringement here was flawed by an unwarranted reading into the claims of that part of the specification devoted to a description of [a process]. . . . Whether Stratoflex employs a different process in forming its inner layer is irrelevant, the sole question being whether the accused . . . product of Stratoflex infringes the product claims of the '087 patent").

Although the development of recombinant technology provides the scientific and commercial communities with innovative techniques for manufacturing certain products and compositions, the patent protection of product claims has not changed. That is, a product claim still protects the use and sale of the product, regardless of whether the product was produced by traditional or recombinant technology. In *Scripps Clinic & Research Foundation* v. *Genentech, Inc.*, 666 F. Supp. 1379 (N.D. Cal. 1987), a case involving a patent covering "[a] human Factor VIII:C preparation having a specific activity greater than 2240 units/mg," *id.* at 1385, the defendant manufactured human Factor VIII:C by recombinant DNA technology. Rejecting the defendant's argument that the product

claims should be limited to Factor VIII:C derived from the disclosed process only, the court stated:

> Scripps is entitled to claim purified Factor VIII:C having the characteristics of human Factor VIII:C, whether derived through its disclosed process or any other process achieving the same result.
>
> . . .
>
> Human Factor VIII:C as claimed in the patent therefore applies to any Factor VIII:C preparation, regardless of how produced, having the same material and functional characteristics as the plasma-derived preparation.

666 F. Supp. at 1390. This principle applies here, and this Court, therefore, ruled that a product patent claim covers that material produced by recombinant technology; if such material falls within the scope of the asserted product claims, then those patent claims are infringed. Infringement of product or composition claims depends upon the equivalence of the product ingredients and upon the substantial similarity of the proportions of those ingredients, not upon the process used to manufacture the product.

Accordingly, because no genuine issues of material fact existed on the question whether the Amgen recombinant erythropoietin infringes the claims of the '195 patent, the Court granted the motions of Chugai and Genetics for partial summary judgment with respect to this particular claim.

B. Patent Misuse.

Chugai also seeks summary judgment on the issue whether Amgen's '008 Patent is unenforceable on the ground that Amgen's institution and continued prosecution of proceedings in the Commission constitutes patent misuse; that is, Amgen is

attempting to enforce the '008 patent as a process patent which, Chugai alleges, is beyond the lawful scope of the patent.[16]

The doctrine of patent misuse is an equitable one, providing an equitable defense to an infringement action. Since, under patent law, a patentee is granted a monopoly of a particular invention, the doctrine of patent misuse prevents that patentee from using the patent as a means of restraining trade in areas beyond the scope of the patent. "[T]he essence of patent misuse consists of an attempt by the patent holder to gain for himself rights not inherent in the patent itself, or to extend his monopoly beyond that legally granted to him." *USM Corp.* v. *Standard Pressed Steel Co.*, 453 F. Supp. 743, 748-49 (N.D. Ill. 1978), *aff'd in part, vacated in part on other grounds sub no. USM*

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[16] As a jurisdictional matter Amgen argues that, under the doctrine of primary jurisdiction, this Court should stay this motion pending the resolution of those issues presented to the Commission. Opposition Memorandum II at 17-19. The doctrine of primary jurisdiction

> applies where a claim is originally cognizable in the courts, and comes into play whenever enforcement of the claim requires the resolution of issues which, under a regulatory scheme, have been placed within the special competence of an administrative body; in such a case the judicial process is suspended pending referral of such issues to the administrative body for its views.

United States v. *Western Pacific R.R. Co.*, 352 U.S. 59, 64, 77 S. Ct. 161 (1956). Although the doctrine may be involved in the appropriate course under different circumstances, *see Ricco* v. *Chicago Mercantile Exchange*, 409 U.S. 289, 305-306, 93 S. Ct. 573 (1973) (upholding the stay of an antitrust suit until the Commodity Exchange Commission could decide whether the defendants had violated the Commodity Exchange Act rules); *Meditech Int'l Co.* v. *Minigrip, Inc.*, 648 F. Supp. 1488, 1496 (N.D. Ill. 1986) (ruling that the doctrine of primary jurisdiction stayed the action until the International Trade Commission resolved whether the defendant misled the Commission), the Court need not stay action on this motion for summary judgment. The issue here is a preliminary one — whether Amgen filed its complaint with the Commission in bad faith — and such an issue does not necessarily require the special competence of the Commission. Moreover, in this opinion, the Court does not bypass the Commission; indeed, as will be explained below, the Court incorporates and relies upon a preliminary determination made by the Commission denying Chugai's motion for summary determination of the Commission complaint. *See infra* note 20. Thus, a stay of this motion is not required in this case.

Corp. v. *SPS Tech., Inc.*, 694 F.2d 505 (7th Cir. 1982), *cert. denied*, 462 U.S. 1107 (1983); *Analytichem Int'l, Inc.* v. *Har-Len Assocs., Inc.*, 490 F. Supp. 271, 274 (W.D. Pa. 1980) (stating that "[t]he basic vice is the attempt to extend the granted monopoly beyond the terms of the grant"). In this context, patent misuse is closely related to the principles of antitrust law. *USM Corp.*, 694 F.2d at 511-12.

The enforcement of patent rights, however, does not constitute, by itself, patent misuse. Section 271(d) of Title 35 of the United States Code provides, in relevant part:

> No patent owner otherwise entitled to relief for infringement or contributory infringement of a patent shall be denied relief or deemed guilty of misuse or illegal extension of the patent right by reason of his having done one or more of the following: . . . (3) sought to enforce his patent rights against infringement or contributory infringement.

See also Carpet Seaming Tape Licensing Corp. v. *Best Seam Inc.*, 616 F. 2d 1133 1143 (9th cir. 1980), *cert. denied*, 469 U.S. 818 (1983). Therefore, an attempted enforcement of a patent must be in bad faith in order to constitute patent misuse. *E.g., id.; cf. Argus Chemical Corp.* v. *Fibre Glass-Evercoat Co.*, 812 F.2d 1381, 1385-86 (Fed. Cir. 1987) (holding that a finding of bad faith is necessary to establish antitrust liability based on patent misuse); *Handgards, Inc.* v. *Ethicon, Inc.*, 743 F.2d 1282, 1289 (9th Cir. 1984) (*Handgards II*) (same), *cert. denied*, 469 U.S. 1190 (1985). "[T]he alleged infringer [must] show that the patentee has impermissibly broadened the 'physical or temporal scope' of the patent grant with anti-competitive effect." *Windsurfing Int'l, Inc.* v. *AMF, Inc.*, 782 F.2d 995, 1001 (Fed. Cir.) (citing *Blonder-Tongue Laboratories, Inc.* v. *Univ. of Illinois Found.*, 402 U.S. 313, 343, 91 S. Ct. 1434, 1450 [1971]), *cert. denied sub nom. BIC*

Leisure Prods., Inc. v. *Windsurfing Int'l, Inc.*, 477 U.S. 905 (1986). Discussing the element of bad faith required by this affirmative defense, the Ninth Circuit, in *Handgards II*, stated:

> Ethicon's antitrust liability is premised upon its prosecution of a patent infringement suit with the knowledge that its patent was invalid. *Handgards I*, 601 F.2d at 994. . . . All that is required for a finding of bad faith in the context of an infringement suit is that the patent holder, Ethicon, knew that its patent was invalid. The bad faith involved — attempting to enforce a government granted monopoly to which the patent holder knows he has no right — is as much extrinsic to the suit as it is inherent in filing a legal cause of action devoid of merit.

Id. at 1289. *See Argus Chem.*, 812 F.2d at 1386 (ruling that "the litigant must establish that the patentee acted in bad faith because he knew that the patent was invalid") (citing *Handgards II*).[17]

In the present case, Chugai broadly asserts that "Amgen has deliberately mischaracterized its patent as claiming a process of manufacturing recombinant [erythropoietin] when, in fact, its own counsel has conceded that all of its process claims met rejection in the [Patent & Trademark Office] and were cancelled from the '008 patent application." Memorandum in Support of Defendant Chugai Pharmaceutical Co., Ltd's Motion for Summary Judgment at 28 (hereinafter, "Chugai Memorandum II"). Chugai, however, bears the burden of demonstrating that

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[17] Although *Handgards II* and *Argus Chem.* both involved actions grounded in antitrust law rather than the doctrine of patent misuse, they are apposite here. The gravamen of both types of actions centers on the bad faith of the patentee. Not surprisingly, courts have determined that the treatment of the bad faith issue in the patent misuse context is largely the same as in antitrust law. *See, e.g., USM Corp.*, 694 F. 2d at 511-12.

no genuine issues of material fact exist on the issue whether Amgen in fact knew that the '008 patent did not cover Chugai's production of recombinant erythropoietin, yet still instituted the proceedings in the Commission. This Court rules that Chugai has not satisfied this burden.

There are a number of reasons that summary judgment on this particular claim is inappropriate at this juncture. As a preliminary matter, Robert D. Weist ("Weist"), senior vice president, general counsel, and secretary of Amgen, asserts that Amgen filed its complaint in the Commission "in the good faith belief that Chugai's importation of recombinant erythropoietin is an unfair act that should be excluded under 19 U.S.C. Secs. 1337 and 1337a."[18] Declaration of Robert D. Weist in Opposition to Defendant's Motion for Summary Judgment at para. 7 (hereinafter, "Weist Decl."). Moreover, as expressed below,[19] whether Chugai's importation of recombinant erythropoietin violates Section 337a of the Tariff Act of 1930 is hardly free from doubt.[20] Therefore, given these factors, this Court cannot rule as matter of law that Amgen instituted the proceedings in the Commission in bad faith.

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[18] In this context, there is a presumption that a patentee's infringement action is brought in good faith. *See Handgards, Inc.* v. *Ethicon, Inc.*, 601 F.2d 986, 996 (9th Cir. 1979) (*Handgards I*), *cert. denied*, 444 U.S. 1025 (1980); *Universal Athletic Sales Co.* v. *American Gym*, 480 F. Supp. 408, 423 (W.D. Pa. 1979).

[19] *See infra* at [A227].

[20] In fact, Chugai filed a motion for summary determination in the Commission proceedings. The Administrative Law Judge, however, denied the motion on March 7, 1988. Thus, where the Commission has denied the motion for summary determination, this Court concludes that there is sufficient evidence to establish a genuine issue of material fact concerning whether the Commission proceeding is a mere sham. *Cf. Omni Resource Dev. Corp.* v. *Conoco, Inc.*, 739 F.2d 1412 (9th Cir. 1984) (Kennedy, J.) (holding that the defendant, the plaintiff in prior state court proceedings, is immune from antitrust liability under the *Noerr-Pennington* doctrine in part because those state court proceedings could not be considered baseless where the state court granted temporary and preliminary injunctions against the subsequent antitrust case plaintiff); *Shepherd Intelligence Systems, Inc.* v. *Defense Tech., Inc.*, No. 87-1101-Y, slip op. at 2 (D. Mass. Dec. 20, 1988) holding that defendants' success in obtaining preliminary injunctive relief in state court was insufficient to establish as matter of law that those state court suits are not baseless).

C. The '008 Patent and Process Claims.

In the alternative, Chugai seeks summary judgment on the issue whether the '008 patent contains process claims. Chugai asserts that the '008 patent does not contain process claims, and therefore it does not cover Chugai's process of manufacturing recombinant erythropoietin.

The background section of the '008 patent describes the invention as relating "generally to the manipulation of genetic materials and, more particularly, to recombinant procedures making possible the production of polypeptides possessing part or all of the primary structural conformation and/or one or more of the biological properties of the naturally-occurring erythropoietin." United States Patent No. 4,703,008 at col. 1 (Complaint, Exhibit A). There are 31 claims contained in the '008 patent, and those claims, in essence, encompass the following inventions: 1) purified and isolated DNA sequences encoding erythropoietin; 2) DNA vectors for transporting such DNA sequences into host cells; and 3) host cells transformed or transfected with such DNA sequences.[21] Chugai thus con-

[21] The Brief Summary portion of the '008 patent describes the patent as follows:

> The present invention provides, for the first time, novel purified and isolated polypeptide products having part or all of the primary structural conformation (i.e., continuous sequence of amino acid residues) and one or more of the biological properties (e.g., immunological properties and in vivo and in vitro biological activity) of naturally-occurring erythropoietin, including allelic variants thereof. These polypeptides are also uniquely characterized by being the product of procaryotic or eucaryotic host expression (e.g., by bacterial, yeast and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis.
>
> . . .
>
> Novel glycoprotein products of the invention include those having a primary structural conformation sufficiently duplicative of that of naturally-occurring (e.g., human) erythropoietin to allow possession of one or more of the biological properties thereof and

tends that the '008 patent claims extend only to the recombinant "starting materials," not the steps or acts involved in recombinant production of erythropoietin. See Memorandum in Support of Defendant Chugai Pharmaceutical Co., Ltd.'s Motion for Summary Judgment at 14-15 (hereinafter, "Chugai Memorandum II").

In the traditional patent framework, a product is wholly separate and distinct from a process. The court in *In re Amtorg Trading Corp.*, 75 F.2d 826 (3d Cir.), *cert. denied sub nom. Int'l AGR Corp.* v. *Amtorg Trading Corp.*, 296 U.S. 576 (1935), observed:

> The distinction between product and process patents is clear and is quite generally understood. The product patent is upon an invented or discovered article; the process patent is upon a method of making an article. It not infrequently happens that in the same letters patent invention is recognized in both the article and the method of making it, but it is the well-settled rule of law that a product patent protects only the product, and that a process patent protects only the process.

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having an average carbohydrate composition which differs from that of naturally-occurring (e.g., human) erythropoietin.

. . . .

Also provided by the present invention are synthetic polypeptides wholly or partially duplicative of continuous sequences of erythropoietin amino acid residues . . . . These sequences, by virtue of sharing primary, secondary or tertiary structural and conformational characteristics with naturally-occurring erythropoietin may possess biological activity and/or immunological properties in common with the naturally-occurring product such that they may be employed as biologically active or immunological substitutes for erythropoietin in therapeutic and immunological processes.

United States Patent No. 4,703,008 at cols. 10-11 (Complaint, Exhibit A).

Id. at 832. Whether a patent protects a product or a process is an important factor in establishing the proprietary and non-proprietary rights in a particular field of technology. The legal and practical consequences of the product patent, as distinguished from the process patent, are described as follows:

> A product patent gives the patentee the right to restrict the use and sale of the product regardless of how and by whom it was manufactured. A process patentee's power extends only to those products made by the patented process. A process patent thus "leaves the field open to ingenious men to invent and to employ other processes."
>
> A sale of a product made by a patented process does not itself infringe the patent; it is the unauthorized use of the process that infringes the patent.

United States v. *Studiengesellschaft Kohle*, 670 F.2d 1122, 1127-28 (D.C. Cir. 1981) (citations omitted).

Developments in biotechnology, however, have created a complex web of proprietary rights issues and have challenged the traditional norms of patent law.[22] In *Diamond* v. *Chak-*

[22] A concern expressed by some authors and scientists is that the increased commercial incentives to protect intellectual property in the area of biotechnology adversely impacts the traditions of open communication with the scientific community. *See* Eisenberg, *Proprietary Rights and the Norms of Science in Biotechnology Research*, 97 Yale L.J. 177, 178 (1987). Some even regard the patent process darkly as "a means of institutionalized secrecy. . . ." *Id.* at 185 n. 37 (citing *Commercialization of Academic Biomedical Research: Hearings Before the Subcomm. on Investigations and Oversight and the Subcomm. on*

rabarty, 447 U.S. 303, 100 S. Ct. 2204 (1980), the Supreme Court ruled that a live, human-made micro-organism is patentable subject matter under 35 U.S.C. sec. 101. *Id.* at 309. Noting that the patent applicant's claim was not to a natural phenomenon, but to a manufactured substance which does not occur in nature, the Supreme Court stated, "[T]he patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility." *Id.* at 310. *See Ex parte Hibberd*, 227 U.S.P.Q. 443 (P.T.O. Bd. Pt. App. & Interferences 1985) (holding that plants, plant seeds and plant tissue cultures constituted patentable subject matter under 35 U.S.C. sec. 101); *Ex parte Allen*, 2 U.S.P.Q.2d 1425, 1426-27 (P.T.O. Bd. Pat. App. & Interferences 1987) (establishing that polyploid oysters produced by the claimed method constitute patentable subject matter under Section 101, and stating that the issue is "whether the subject matter is a non-naturally occurring manufacture or composition of matter"). These cases, however, address the patentability of certain "manufactures" or "compositions of matter," not the processes of recombinant engineering.

In the instant case, this Court is asked to consider whether the '008 patent encompasses process claims. As previously discussed, the scope of the '008 patent claims can be ascertained as matter of law from the language of the claims, the patent specification, and the prosecution history.[23] Therefore,

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Science, Research and Technology of the House Comm. on Science and Technology, 97th Cong., 1st Sess. 79 [1981]). Although traditional patent law doctrines restricted patent protection to applied technology, as distinguished from basic scientific research, *Diamond* v. *Chakrabarty*, 447 U.S. 303, 100 S. Ct. 2204 (1980) and its progeny have extended patent protection for biotechnical innovations. Eisenberg, *supra*, at 185-90. Eisenberg suggests that the possibility of such protection poses for the inventor an apparent conflict between the scientific norms of promoting the progress of science and the commercial incentives created by scientific rewards. *Id.* at 230.

[23] *See supra* at [A202-A203].

the issue whether the '008 patent covers Chugai's process of manufacturing recombinant erythropoietin must be first analyzed in light of the claims of the patent.

Amgen directs the Court to the following claims of the '008 patent:

> 4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2 or 3 in a manner allowing the host cell to express erythropoietin.
>
> . . .
>
> 23. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 7, 8 or 11 in a manner allowing the host cell to express [a polypeptide similar to erythropoietin].

United States Patent No. 4,703,008 at col. 40 (Complaint, Exhibit A). Although the '008 patent contains claims covering a host cell manipulated in a manner allowing the host cell to express erythropoietin, it is not clear to this Court that such claims are in fact process claims. It is ambiguous whether what is covered here is a product ("[a] procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence") or the process of producing such a cell (transformation or tranfection "*in a manner* allowing the host cell to express erythropoietin"). In view of this ambiguity, therefore, the Court must look to the other factors of claim construction — in particular, the prosecution history — to construe these claims.

The prosecution history of the '008 patent is telling. Amgen's initial patent application contained the following process claims:

> 69. A process for the production of a polypeptide having part or all of the primary structural conformation and one or more of the biological activities

of naturally-occurring erythropoietin, said process comprising:

growing, under suitable nutrient conditions, procaryotic or eucaryotic host cells transformed or transfected with a DNA vector according to claim 62, and isolating desired polypeptide products of the expression of DNA sequences in said vector.

70. A process for the production of a polypeptide having part or all of the primary structural conformation and one or more of the biological activities of naturally-occurring erythropoietin, said process comprising:

growing, under suitable nutrient conditions, procaryotic or eucaryotic host cells transformed or transfected with a DNA vector according to claim 63, and isolating desired polypeptide products of the expression of DNA sequences in said vector.

71. A process for the production of a polypeptide having part or all of the primary structural conformation and one or more of the biological activities of naturally-occurring erythropoietin, said process comprising:

growing, under suitable nutrient conditions, procaryotic or eucaryotic host cells transformed or transfected with a DNA vector according to claim 65, and isolating desired polypeptide products of the expression of DNA sequences in said vector.

72. A process for the production of a polypeptide having part or all of the primary structural conformation and one or more of the biological activities of naturally-occurring erythropoietin, said process comprising:

growing, under suitable nutrient conditions, procaryotic or eucaryotic host cells transformed or

> transfected with a DNA vector according to claim 67, and isolating desired polypeptide products of the expression of DNA sequences in said vector.

'008 File Wrapper Excerpts at 170-71 (Chugai Memorandum II, Exhibit D). Thereafter, on February 4, 1987, the Patent and Trade Office rejected these claims, stating:

> Claims 69-72 are rejected under 35 U.S.C. 103 as being unpatentable over Talmadge et al [sic] and who disclose the basic process of recombinantly expressing and isolating polypeptides as claimed herein [sic]. Even where it is considered that one or more of the starting materials is novel, the application of an old process to such materials to produce the expected result would still be obvious within the meaning of 34 U.S.C. 103; In re Durden, supra; In re Larsen, 141 U.S.P.Q. 730 (1964). Whether or not a product produced by the claimed process possesses any unique or unexpected properties is not material to the question of whether or not the process itself would have been obvious.

'008 File Wrapper Excerpts at 307 (Chugai Memorandum II, Exhibit D). In fact, Amgen characterized those claims 69-72 as "processes for the production of polypeptides through use of claimed transformed or transfected [host cells]." '008 File Wrapper Excerpts at 172 (Chugai Memorandum II, Exhibit D).

Thereafter, in Applicant's Amendment and Reply Under 37 C.F.R. secs. 1.111 and 1.115 filed March 12, 1987, Amgen cancelled claims 14, 15, 17-36, 58, and 61-72 without prejudice and entered new claims, 73-103. In doing so, Amgen stated:

> Citing to the authority of the decisions of *In re Durden* and *In re Albertson*, the Examiner rejected claims

> 69-72 as being directed to obvious methods in view of the DNA expression systems described in Talmadge, et al.
>
> As previously noted Applicant has sought cancellation *without prejudice* of prior claims 69-72 and has not inserted claims corresponding thereto in this amendment. The issues raised by the rejection are no longer present in the application.

'008 File Wrapper Excerpts at 27 (footnote omitted) (emphasis in original) (Chugai Memorandum II, Exhibit D). Moreover, in its communication with the Commission, Amgen apparently does not dispute that the Patent and Trademark Office rejected those claims "specifically in process form for the use of its already-patented host cells to manufacture recombinant erythropoietin." Letter from Dennis Allegretti to Dr. Cheri M. Taylor, Int'l Trade Comm., at 1 (Jan. 21, 1988) (hereinafter, "Allegretti Letter") (Chugai Memorandum II, Exhibit G).[24] Upon this history of prosecuting the claims under this patent, the Patent and Trademark Office issued the '008 patent.

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[24] In the same letter to the Commission, Dennis Allegretti ("Allegretti"), counsel for Amgen, stated:

> [S]uch claims were rejected by the [Patent and Trademark Office] under authority of *In re Durden*.
>
> . . .
>
> Regardless of the hope that may have been offered for the allowance of such process claims after *In re Durden* and prior to the rejection in the Amgen application, regardless of whatever changes in rejection practice and policy by the [Patent and Trademark Office] may arise after that rejection, and regardless of Amgen's continuing efforts to secure process claims in its presently pending continuation application, I submit that the controlling fact is that Amgen's vigorous efforts to secure the allowance of process claims in its original application for the '008 patent, from its filing in 1984 until rejection in 1987, were denied under the authority of *In re Durden*.

Allegretti Letter at 1, 2-3 (Chugai Memorandum II, Exhibit G).

Under the doctrine of prosecution history estoppel, a patentee is precluded from obtaining a claim construction in an infringement action where such an interpretation would "resurrect subject matter surrendered during prosecution of his patent application." *Thomas & Betts Corp.* v. *Litton Systems, Inc.*, 720 F.2d 1572, 1579 (Fed. Cir. 1983). That is,

> [W]here a patentee has, during prosecution before the [Patent and Trademark Office], amended his claims to add a limitation (or cancelled claims containing such a limitation) to overcome a rejection and obtain a patent, he is estopped from later contending in an infringement action that the claims should be interpreted as if that limitation were not present.

Square Liner 360 Degrees, Inc. v. *Chisum*, 691 F.2d 362, 370 (8th Cir. 1982); *see Graham* v. *John Deere Co.*, 383 U.S. 1, 33-34, 86 S. Ct. 684 (1966); *Schriber-Schroth Co.* v. *Cleveland Trust Co.*, 311 U.S. 211, 218, 61 S. Ct. 235 (1940); *Townsend Eng'g Co.* v. *Hitec Co.*, 829 F.2d 1086, 1090-91 (Fed. Cir. 1987); *Thomas & Betts Corp.*, 720 F.2d at 1579; *Hughes Aircraft Co.* v. *United States*, 717 F.2d 1351, 1362-63 (Fed. Cir. 1983). *See generally* 6 E. Lipscomb, *Walker on Patents* sec. 21:10, at 287-97 (3d ed. 1987).

The doctrine of prosecution history estoppel applies to the construction of claims 4 and 23 of the '008 patent. Claims 69-72, which involved "a process for the production of a polypeptide" were all rejected by the Patent and Trademark Office under the authority of *In re Durden*, 763 F.2d 1406 (Fed. Cir. 1985). Amgen then cancelled these claims and amended its '008 patent application. Given the Patent and Trademark Office's rejection of those process claims and Amgen's subsequent cancellation of such claims and the simi-

larity of these claims to a process interpretation"[25] of claims 4 and 23, this Court rules that the '008 patent does not contain any process claims; specifically, the '008 patent does not contain a process claim covering the process of manufacturing recombinant erythropoietin.

This ruling, however, is limited. This Court expressly eschews resolution — on this record — of certain of the other issues in this dispute. First, this Court's ruling does not determine whether the '008 patent covers Chugai's process of manufacturing recombinant erythropoietin. It is clear that if Chugai used host cells covered by the claims of the '008 patent in its production of recombinant erythropoietin, and such production was conducted in the United States, such use would constitute an infringement of the '008 patent. *See Roche Prods. Inc.* v. *Bolar Pharmaceutical Co.*, 733 F.2d 858, 861-63 (Fed. Cir.), *cert. denied*, 469 U.S. 856 (1984). Sufficient facts are not presently before the Court to permit a decision whether Chugai has infringed the product claims contained in the '008 patent.

More importantly, the Court does not decide whether Chugai's importation of recombinant erythropoietin violates Section 337 of the Tariff Act of 1930 (19 U.S.C. sec. 1337) and 19 U.S.C. sec. 1337a. Indeed, only the Commission, and not this Court, is conferred jurisdiction by these statutes. *E.g.*, *Ashlow Ltd.* v. *Morgan Constr. Corp.*, 672 F.2d 371, 375; (4th Cir., 1882) (per curiam); *Telectronics Proprietary, Ltd.* v. *Medtronic, Inc.*, 687 F. Supp. 832, 846 n.42 (S.D.N.Y. 1988) (citing *Ashlow, Ltd.*, 672 F.2d at 372); *Meditech Int'l Co.* v. *Minigrip, Inc.*, 648 F. Supp. 1488, 1493-94 (N.D. Ill. 1986); *In re Convertible Rowing Exerciser Patent Litigation*, 616 F. Supp. 1134, 1140 (D. Del. 1985); *Enka B. V.* v. *E.I. DuPont de Nemours*, 519 F. Supp. 356, 362 n.8 (D. Del. 1981); *see also Tompkins Seals, Inc.* v. *The West Co.*, No.

[25] That is, an interpretation of claims 4 and 23 that treats them as process, not product, claims.

85-4929 (E.D. Pa. 1985) (1985 WESTLAW 4952 at 4). Moreover, although this Court ruled that the '008 patent contains no process claims covering the process of manufacturing recombinant erythropoietin, the '008 patent was construed exclusively within the framework of patent law. It may well be that the word "process" in 19 U.S.C. sec. 1337a, which section provides that "[t]he importation for use, sale, or exchange of a product made, produced, processed, or mined under or by means of a process covered by the claims of any unexpired valid United States letters patent, shall have the same status . . .," should be interpreted more broadly than the above interpretation of "process" made by this Court in the context of patent law. On this issue, however, that Court expresses no opinion.

Accordingly, the Court GRANTED the motion of Chugai and Genetics for partial summary judgment on the claim that Amgen infringes the '195 patent. The Court also GRANTS the motion of Chugai for partial summary judgment on the claim that the '008 patent does not contain a process claim.

/s/WILLIAM G. YOUNG
UNITED STATES DISTRICT JUDGE

APPENDIX D

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF MASSACHUSETTS

AMGEN INC.,
Plaintiff,

v. CIVIL ACTION NO. 87-2617-Y

CHUGAI PHARMACEUTICAL CO., LTD.
and GENETICS INSTITUTE, INC.,
Defendants. Judge William G. Young

JUDGMENT

This action having been tried before the Court without a jury, the Honorable Patti B. Saris, United States Magistrate, presiding, and the Court having heard the testimony, examined the other evidence presented by the parties, considered the arguments of counsel and the briefs submitted by each of the parties, and a Memorandum and Order setting forth the Court's findings of fact and conclusions of law having been rendered,

IT IS ORDERED AND ADJUDGED:

1. Genetics Institute, Inc. ("GI") is the owner of United States Letters Patent No. 4,677,195, granted June 30, 1987 to Rodney M. Hewick and entitled "Homogeneous Erythropoietin" ("'195 patent").

2. Chugai Pharmaceutical Co., Ltd. ("Chugai") is the exclusive licensee of the '195 patent and has the right to maintain this action for infringement.

3. Amgen, Inc. is the owner of United States Letters Patent No. 4,703,008, granted on October 27, 1987, to Fu-Kuen Lin and entitled "DNA Sequences Encoding Erythropoietin" (" '008 patent").

4. This Court has jurisdiction of the parties and the subject matter of this action.

'008 Patent Issues

5. Claims 2, 4 and 6 of the '008 patent are valid and enforceable and have been infringed by GI.

6. The infringement of the '008 patent by GI prior to the Court's Memorandum and Order of December 11, 1989, was not willful.

7. Claims 7, 8, 23, 24, 25, 26, 27 and 29 of the '008 patent are invalid for lack of enablement under 35 U.S.C. § 112 but, if valid, were infringed by GI.

8. The '008 patent does not contain a process claim.

9. Chugai has not infringed, contributorily infringed or induced infringement of any claim of the '008 patent.

10. Amgen's complaint against Chugai is dismissed.

'195 Patent Issues

11. Claims 1 and 3 of the '195 patent are valid and enforceable and have been infringed by Amgen.

12. Amgen has not infringed claims 2 and 5 of the '195 patent.

13. The infringement of the '195 patent by Amgen prior to the Court's Memorandum and Order of December 11, 1989, was not willful.

14. Claims 4 and 6 of the '195 patent are invalid for indefiniteness under 35 U.S.C. § 112, but, if valid, were infringed by Amgen.

15. Amgen did not misuse the '008 patent by its participation in, or institution of investigations by and before the United States International Trade Commission into Chugai's importation of erythropoietin into the United States.

16. This is not an "exceptional" case under 35 U.S.C. § 285 warranting an award of attorneys fees, costs and expenses to any party, and each party shall bear its own costs, expenses and attorneys fees.

17. The Court expressly determines that there is no just reason for delay in the entry of this judgment until a final determination of all of the claims and liabilities of the parties. Consistent with the foregoing determination and the provisions of 28 U.S.C. § 1292(c)(2), this judgment shall be entered as a final judgment pursuant to Rule 54(b), Fed. R. Civ. P., and the Clerk is directed to enter this judgment as final forthwith.

DATED: March 14, 1990

/s/ William G. Young
WILLIAM G. YOUNG
UNITED STATES DISTRICT JUDGE

APPENDIX E

United States Court of Appeals for the Federal Circuit

90-1273, -1275

AMGEN, INC.,
Plaintiff/Cross-Appellant,

v.

CHUGAI PHARMACEUTICAL CO., LTD.,
and GENETICS INSTITUTE, INC.,
Defendants-Appellants.

ORDER

Before MARKEY, Circuit Judge, LOURIE, Circuit Judge, CLEVENGER, Circuit Judge.

A petition for rehearing having been filed in this case,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for rehearing be, and the same hereby is, denied.

The suggestion for rehearing in banc is under consideration.

The mandate will issue on April 5, 1991.

FOR THE COURT,

Dated: April 2, 1991

/s/ Francis X. Gindhart
Francis X. Gindhart
Clerk

APPENDIX F

Amgen's U.S. Patent 4,703,008

EXAMPLE 10

In the previous examples, recombinant monkey or human EPO material was produced from vectors used to transfect COS-1 cells. These vectors replicate in COS-1 cells due to the presence of SV40 T antigen within the cell and an SV40 origin of replication on the vectors. Though these vectors produce useful quantities of EPO in COS-1 cells, expression is only transient (7 to 14 days) due to the eventual loss of the vector. Additionally, only a small percentage of COS-1 became productively transfected with the vectors. The present example describes expression systems employing Chinese hamster ovary (CMO) DHFR - cells and the selectable marker, DHFR. [For discussion of related expression systems, see U.S. Pat. No. 4,399,216 and European Patent Application Nos. 117058, 117059 and 117060, all published Aug. 29, 1984.]

CHO DHFR - cells (DuX-B11) CHO K1 cells. Urlaub, et al., *Proc. Nat. Acad. Sci (U.S.A.),* Vol. 77,4461 (1980) lack the enzyme dihydrofolate reductase (DHFR) due to mutations in the structural genes and therefore require the presence of glycine, hypoxanthine, and thymidine in the culture media. Plasmids pDSVL-MkE (Example 6) or pDSVL-gHuEPO (Example 7B) were transfected along with carrier DNA into CHO DHFR - cells growing in media containing hypoxanthine, thymidine, and glycine in 60 mm culture plates. Plasmid pSVgHuEPO (Example 7A) was mixed with the plasmid pMG2 containing a mouse dihydrofolate reductase gene cloned into the bacterial plasmid vector pBR322 (per Gasser, et al., supra). The plasmid mixture and carrier DNA was transfected into CHO

DHFR-cells. (Cells which acquire one plasmid will generally also acquire a second plasmid). After three days, the cells were dispersed by trypsinization into several 100 mm culture plates in media lacking hypoxanthine and thymidine. Only those cells which have been stably transformed with the DHFR gene, and thereby the EPO gene, survive in the media. After 7-21 days, colonies of surviving cells became apparent. These transformant colonies, after dispersion of trypsinization can be continuously propagated in media lacking hypoxanthine and thymidine, creating new cell strains (e.g., CHO pDSVL-MkEPO, CHO pSVgHuEPO, CHO-pDSVL-gHuEPO).

Culture fluids from the above cell strains were tested in the RIA for the presence of recombinant monkey or human EPO. Media for strain CHO pDSVL-MkEPO contained EPO with immunological properties like that obtained from COS-1 cells transfected with plasmid pDSVL-MkEPO. A representative 65 hour culture fluid contained monkey EPO at 0.60 U/ml.

Culture fluids from CHO pSVgHuEPO and CHO pDSVL-gHuEPO contained recombinant human EPO with immuological properties like that obtained with COS-1 cells transfected with plasmid pSVgHuEPO or pDSVL-gHuEPO. A representative 3 day culture fluid from CHO pSVgHuEPO contained 2.99 U/ml of human EPO and a 5.5 day sample from CHO pDSVL-gHuEPO had 18.2 U/ml of human EPO as measured by the RIA.

The quantity of EPO produced by the cell strains described above can be increased by gene amplification given new cell strains of greater productivity. The enzyme dihydrofolate reductase (DHFR) which is the product coded for by the DHFR gene can be inhibited by the drug methotrexate (MTX). More specifically, cells propagated in media lacking hypoxanthine and thymidine are inhibited or killed by MTX. Under the appropriate conditions, (e.g., minimal concentrations of MTX) cells resistant to and able to grow in MTX can be obtained.

These cells are found to be resistent to MTX due to an amplification of the number of their DHFR genes, resulting in increased production of DHFR enzyme. The surviving cells can, in turn, be treated with increasing concentrations of MTX, resulting in cell strains containing greater numbers of DMFR genes. "Passenger genes" (e.g., EPO) carried on the expression vector along with the DHFR gene or transformed with the DHFR gene are frequently found also to be increased in their gene copy number.

As examples of practice of this amplification system, cell strain CMO pDSVL-MkE was subjected to increasing MTX concentrations (O nM, 30 nM and 100 nM). Representative 65-hour culture media samples from each amplification step were assayed by RIA and determined to contain 0.60, 2.45 and 6.10 U/ml, respectively. Cell strain CHO pDSVL-gHuEPO was subjected to a series of increasing MTX concentrations of 30 nM, 50 nM, 100 nM, 200 nM, 1 *m*M, and 5 *m*M MTX. A representative 3-day culture media sample from the 100 nM MTX step contained human EPO at 3089 ± 129 u/ml as judged by RIA. Representative 48 hour cultural medium samples from the 100 nM and 1 *m*M MTX steps contained, respectively, human EPO at 466 and 1352 U/ml as judged by RIA (average of triplicate assays). In these procedures 1×10^6 cells were plated in 5 ml of media in 60 mm culture dishes. Twenty-four hours later the media were removed and replaced with 5 ml of serum-free media (high glucose DMEM supplemented with 0.1 mM non-essential amino acids and L-glutamine). EPO was allowed to accumulate for 48 hours in the serum-free media. The media was collected for RIA assay and the cells were trypsinized and counted. The average RIA values of 467 U/ml and 1352 U/ml for cells grown at 100 nM and 1 *m*M MTX, respectively, provided actual yields of 2335 U/plate and 6750 U/plate. The average cell numbers per plate were 1.94×10^6 and 3.12×10^6 cells,

respectively. The effective production rates for these culture conditions were thus 1264 and 2167 U/10^4 cells/48 hours.

The cells in the cultures described immediately above are a genetically heterogeneous population. Standard screening procedures are being employed in an attempt to isolate genetically hemogeneous clones with the highest production capacity. See, Section A, Part 2, of "Points to Consider in the Characterization of Cell Lines Used to Produce Biologics", June 1, 1984. Office of Biologics Research Review, Center for Drugs and Biologics, U.S. Food and Drug Administration.

The productivity of the EPO producing CHO cell lines described above can be improved by appropriate cell culture techniques. The propagation of mammalian cells in culture generally requires the presence of serum in the growth media. A method for production of erythropoietrin from CHO cells in media that does not contain serum greatly facilities the purification of erythropoletin from the culture medium. The method described below is capable of economically producing erythropoietin in serum-free media in large quantities sufficient for production.

Strain CHO pDSVL-gHuEPO cells, grown in standard cell culture conditions, are used to seed spinner cell culture flasks. The cells are propagated as a suspension cell line in the spinner cell culture flask in media consisting of a 50 - 50 mixture of high glucose DMEM and Ham's F12 supplemented with 5% fetal calf serum, L-glutamine, Penicillin and Streptopmycin, 0.05 mM non-essential amino acids and the appropriate concentration of methotrexate. Suspension cell culture allows the EPO-producing CHO cells to be expanded easily to large volumes. CHO cells, grown in suspension, are used to seed roller bottles at an initial seeding density of 1.5×10^7 viable cells per 850 cm^2 roller bottle in 200 ml of media. The cells are allowed to grow to confluency as an adherent cell line over a three-day period. The media used for this phase of the growth is

the same as used for growth in suspension. At the end of the three-day growth period, the serum containing media is removed and replaced with 100 ml of serum-free media; 50-50 mixture of high glucose DMEM and Ham's F12 supplemented with 0.05 mM non-essential amino acids and L-glutamine. The roller bottles are returned to the roller bottle incubator for a period of 1-3 hours and the media again is removed and replaced with 100 ml of fresh serum-free media. The 1-3 hour incubation of the serum-free media reduces the concentration of contaminating serum proteins. The roller bottles are returned to the incubator for seven days during which erythropoietin accumulates in the serum-free culture media. At the end of the seven-day production phase, the conditioned media is removed and replaced with fresh serum-free medium for a second production cycle. As an example of the practice of this production system, a representative seven-day, serum-free media sample contained human erythropoietin at 3892 ± 409 U/ml as judged by the RIA. Based on an estimated cell density of 0.9 to 1.8 × 10^5 cells/cm^2, each 850 cm^2 roller bottle contained from 0.75 to 1.5 x 10^5 cells and thus the rate of production of EPO in the 7-day, 100 ml culture was 750 to 1470 U/10^6 cells/48 hours.

Culture fluids from cell strain CMO pDSVL-MkEPO carried in 10 nM MTX were subjected to RIA in vitro and in vivo EPO activity assays. The conditioned media sample contained 41.2 ± 1.4 U/ml of MkEPO as measured by the RIA, 41.2 ± 0.064 U/ml as measured by the in vitro biological activity assay and 42.5 ± 5 U/ml as measured by the in vivo biological activity assay. Amino acid sequencing of polyeptide products revealed the presence of EPO products, a principle species having 3 residues of the "leader" sequence adjacent the putative amino terminal alanine. Whether this is the result of incorrect membrane processing of the polypeptide in CHO cells or reflects a difference in structure of the amino terminus of monkey EPO vis-a-vis human EPO, is presently unknown.

Culture fluids from cell strain CHO pDSVL-gHuEPO were subjected to the three assays. A 5.5. day sample contained recombinant human EPO in the media at a level of 18.2 U/ml by RIA assay, 15.8 ± 4.6 U/ml by in vitro assay and 16.8 ± 3.0 U/ml by in vivo assay.

Culture fluid from CHO pDSVL-gHuEPO cells prepared amplified by stepwise 100 nM MTX were subjected to the three assays. A 3.0 day sample contained recombinant human EPO at a level of 3089 ± 129 U/ml by RIA, 2589 ± 71.5 U/ml by in vitro assay, and 2040 ± 160 U/ml by in vivo assay. Amino acid sequencing of this product reveals an amino terminal corresponding to that designated in FIG. 6.

Cell conditioned media from CHO cells transfected with plasmid pDSVL-MkE in .10 nM MTX were pooled, and the MTX dialyzed out over several days, resulting in media with an EPO activity of 221 ± 5.1 U/ml (EPO-CCM). To determine the in vivo effect of the EPO-CCM upon hematocrit levels in normal Balb/C mice, the following experiment was conducted. Cell conditioned media from untransfected CHO cells (CCM) and EPO-CCM were adjusted with PBS. CCM was used for the control group (3 mice) and two dose levels of EPO-CCM — 4 units per injection and 44 units per injection — were employed for the experimental groups (2 mice/group). Over the course of 5 weeks the seven mice were injected intraperistoneally, 3 times per week. After the eighth injection, average hematocrit values for the control group were determined to be 50.4%; for the 4U group, 55.1%; and, for the 44U group. 67.9%.

Mammalian cell expression products may be readily recovered in substantially purified form from culture media using HPLC (C_4) employing an ethanol gradient, preferably at pH7.

A preliminary attempt was made to characterize recombinant glycoprotein products from conditioned medium of COS-1 and CHO cell expression of the human EPO gene in comparison to

human urinary EPO isolates using both Western blot analysis and SDS-PAGE. These studies indicated that the CHO-produced EPO material had a somewhat higher molecular weight than the COS-1 expression product which, in turn, was slightly larger than the pooled source human urinary extract. All products were somewhat heterogeneous. Neuraminidase enzyme treatment to remove sialic acid resulted in COS-1 and CHO recombinent products of approximately equal molecular weight which were both nonetheless larger than the resulting asialo human urinary extract. Endoglycosidase F enzyme (EC 3.2.1) treatment of the recombinant CHO product and the urinary extract product (to totally remove carbohydrate from both) resulted in substantially homogeneous products having essentially identical molecular weight characteristics.

Purified human urinary EPO and a recombinant, CHO cell-produced, EPO according to the invention were subjected to carbohydrate analysis according to the procedure of Ledeen, et al. *Methods in Enzymology*, 83 (*Part D*), 139-191 (1982) as modified through use of the hydrolysis procedures of Nesser, et al., *Anal. Biochem.*, 142, 58-67 (1984). Experimentally determined carbohydrate constitution values (expressed as molar ratios of carbohydrate in the product) for the urinary isolate were as follows: Hexoses, 1.73, N-acetylglucosamine, 1; N-acetylneuraminic acid, 0.93; Fucose, 0; and N-acetylgalactosamine, 0. Corresponding values for the recombinant product (derived from CHO pDSVI-gHuEPO 3-day culture media at 100 nM MTX) were as follows: Hexoses, 15.09; N-acetylglucosamine, 1; N-acetylneuraminic acid, 0.998; Fucose, 0; and N-acetylgalactosamine, 0. These findings are consistent with the Western blot and SDS-PAGE analysis described above.

Glycoprotein products provided by the present invention are thus comprehensive of products having a primary structural conformation sufficiently duplicative of that of a naturally-

occurring erythropoietin to allow possession of one or more of the biological properties thereof and having an average carbohydrate composition which differs from that of naturally-occurring erythropoietin.

APPENDIX G

The Patent Clause, Art. I, § 8, cl. 8 provides:

> The Congress shall have Power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.

35 U.S.C. § 112 provides in relevant part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 114 provides in relevant part:

> When the invention relates to a composition of matter, the Commissioner [of the Patent Office] may require the applicant to furnish specimens or ingredients for the purpose of inspection or experiment.

35 U.S.C. § 282 provides in relevant part:

> The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity. The following shall be defenses in

any action involving the validity or infringement of a patent and shall be pleaded:

. . .

(3) Invalidity of the patent or any claim in suit for failure to comply with any requirement of sections 112 or 251 of this title.

Fed.R.Civ.P. 52(a) provides in relevant part:

Findings or fact, whether based on oral or documentary evidence, shall not be set aside unless clearly erroneous, and due regard shall be given to the opportunity of the trial court to judge the credibility of the witnesses.